

CHAPTER 1

CLASSIFICATION AND DIAGNOSIS OF DIABETES

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SUMMARY

The classification of diabetes was originally limited to only two categories called juvenile-onset diabetes mellitus, now known as type 1 diabetes mellitus, and adult-onset diabetes mellitus, now known as type 2 diabetes mellitus. This has grown to a recognition of more than 50 subcategories caused by various pathogenic mechanisms or accompanying other diseases and syndromes. The diagnosis of diabetes has evolved from physician recognition of typical symptoms to detection of ambient hyperglycemia and, thence, to the definition of excessive plasma glucose levels after an overnight fast and/or following challenge with a glucose load (oral glucose tolerance test or OGTT), and more recently, by measurement of glycosylated hemoglobin (A1c). Screening has uncovered a much higher prevalence of diabetes in the United States and elsewhere, as well as its enormous public health impact. Modern testing has defined individuals at high risk for the development of diabetes and pregnant women whose fetuses are at increased risk for mortality and morbidity.

Type 1 diabetes results from an autoimmune attack on the pancreatic islet beta cells, manifest by autoantibodies and T cells reactive with islet cell antigens prior to and after the development of hyperglycemia. When approximately 80% of beta cells have been damaged or destroyed, insulin deficiency produces hyperglycemia and risk of ketosis. Hyperglycemia, in turn, causes osmotic diuresis resulting in frequent urination, thirst, and weight loss. Type 2 diabetes is caused by a combination of insulin resistance and relative insulin insufficiency. Insulin resistance accompanies obesity, a sedentary lifestyle, and advanced age. The pathogenetic factors of type 1 and type 2 diabetes overlap in many patients, with obesity now prevalent in children and adults. Gestational diabetes is specific for pregnancy and is a harbinger of future type 2 diabetes.

Diagnostic glycemic criteria for presymptomatic diabetes have been set using diabetic retinopathy as a specific complication of the disease: A1c $\geq 6.5\%$; fasting plasma glucose (FPG) ≥ 126 mg/dL; or plasma glucose measured 2 hours after an OGTT (2-hour PG) ≥ 200 mg/dL. For patients with typical symptoms, a random plasma glucose ≥ 200 mg/dL is diagnostic. The 2-hour PG yields the highest prevalence and A1c the lowest. A1c is the most convenient and practical test, requiring no preparation, is analytically superior, and has the lowest intraindividual variation. It is more expensive than the FPG, but the same or less than the OGTT. The 2-hour PG is the most burdensome to the patient and has the highest intraindividual variation. Standardized measurement of A1c is not available everywhere. Confirmation of an abnormal test with the same test is recommended.

Studies in various populations show inconsistency among the glycemic tests. Of people meeting the A1c criterion, 27%–98% meet plasma glucose criteria. Of people meeting plasma glucose criteria, 17%–78% meet the A1c criterion. These discrepancies occur because each test measures different aspects of hyperglycemia that may vary among patients. While the risk of future diabetes is continuously associated with plasma glucose and A1c, the areas between the upper limits of normal and the diabetes cutpoints have been called “prediabetes” or “high risk for diabetes.” These have been defined categorically as A1c 6.0%–6.4% or 5.7%–6.4%; impaired fasting glucose (IFG), FPG 100–125 mg/dL; and impaired glucose tolerance (IGT), 2-hour PG 140–199 mg/dL. A1c 6.0%–6.4% increases the odds ratio (OR) for progression to diabetes (OR 12.5–16) more than the range of 5.7%–6.4% (OR 9.2).

In U.S. studies, the incidence of type 2 diabetes averages approximately 6% per year in people with IGT and can reverse spontaneously. IFG is more prevalent than IGT in the United States, though IGT rises more sharply with age. IFG increases the risk of future diabetes to various degrees in different countries, with odds ratios ranging from 2.9 to 18.5.

Opportunistic screening for diabetes in health care venues, especially if targeted to persons with high-risk characteristics, e.g., obesity and older age, can be cost-effective. The lower cutpoints for prediabetes should be used if the screening is also aimed at those at high

risk for developing diabetes. Indiscriminate public screening for diabetes is not yet supported by sufficient long-term benefit gained from early detection of asymptomatic diabetes, nor has its cost-effectiveness been demonstrated. However, if undertaken, a capillary blood glucose ≥ 120 mg/dL is an efficient screening cutpoint with relatively low cost per case detected.

The major public health implication of diagnosing asymptomatic diabetes is that diabetes is a major cause of cardiovascular disease, renal failure requiring dialysis and kidney transplant, and blindness or vision-threatening retinal disease necessitating surgery or intraocular injection therapy. With appropriate targeted therapy of hyperglycemia, hypertension, and dyslipidemia, these complications can be prevented or ameliorated.

INTRODUCTION

Diabetes is a complex metabolic disorder consisting of two main types: type 1, comprising approximately 5% of diabetes, and type 2, comprising 90%–95% (1). The prevalence of diabetes, especially type 2 diabetes, is rising in the United States, associated with increased prevalence of obesity, vulnerable minorities, and aging, in the setting of polygenic risk. While the annual incidence in the United States may have plateaued in recent years, the epidemic of diabetes and its risk factors occur worldwide (2,3,4). Although carbohydrate metabolism is most obviously deranged and is the basis for biochemical tests of the diagnosis, fat metabolism is also adversely affected, and abnormalities in protein metabolism, though more subtle, also exist. For example, fasting free fatty acid and triglyceride levels are elevated, and tissue uptake of amino acids, especially branch chain amino acids, in response to insulin is impaired.

The derangements in carbohydrate metabolism that characterize diabetes are clinically recognizable by patients when plasma glucose elevations reach levels that cause glycosuria and polyuria with resultant polydipsia. These symptoms may not occur early in type 2 diabetes owing to the slow, progressive rise in glycemia over time, and when present, they generally

are relieved by nutritional and pharmacological therapy. By contrast, the onset of type 1 diabetes is clinically abrupt and usually requires immediate initiation of insulin therapy. In both types, hyperglycemia causes the later development of “diabetic complications,” the morbidity and mortality of which dominate the clinical picture and fate of diabetic individuals, as well as the economic costs of diabetes in the United States, which amounted to \$245 billion in 2012 (5).

While the clinical recognition of diabetes has existed for many centuries, its linkage to high levels of glucose in the blood and urine is more recent and has permitted development of increasingly sophisticated tests for the disease. Excessive levels of glucose now reliably identify individuals at risk for the serious and lethal complications of diabetes. This has placed a premium on glucose-based diagnostic tests with cutpoints that predict an increased risk of retinopathy, the most specific of the diabetic complications.

This chapter is composed of two main sections. The first section presents an updated classification of diabetes with numerous subtypes that are characterized by their clinical contexts, phenotypes, variable clinical courses, and pathophysiologies. A category of

“prediabetes” or “high risk for diabetes,” better defined for type 2 diabetes than for type 1 diabetes, has been added to the classification as well.

The second major section deals with the diagnosis of and screening for diabetes. The most recent test, measurement of glycated hemoglobin (A1c), is popular for its practicality, reflection of glycemia for months rather than hours, and analytical precision. An A1c level $\geq 6.5\%$ (≥ 48 mmol/mol) is recognized by the American Diabetes Association (ADA), an International Expert Committee (IEC), and the World Health Organization as diagnostic for diabetes. Criteria for diagnosis using plasma glucose measured in the fasting state (≥ 126 mg/dL [6.99 mmol/L]) and 2 hours after an oral glucose load (≥ 200 mg/dL [≥ 11.10 mmol/L]) are also presented and compared with the A1c criterion with regard to sensitivity and specificity for detecting diabetes. The criteria defining the category “high risk for diabetes” vary somewhat among the promulgating groups.

Screening for previously unknown diabetes in both health care venues and public venues is presented using the various tests. The potential benefits and risks of screening are discussed.

CLASSIFICATION OF DIABETES

Diabetes is not a single disease but rather a syndrome characterized by hyperglycemia, and over time, by increased risk of damage to eyes, kidneys, and nerves and, less specifically, to heart and medium and large caliber blood vessels. Diabetes can be divided into four major types: type 1,

type 2, gestational, and secondary or other specific types of diabetes (6). The vast majority of patients comprise the first two types, and over the years, many other names have been used, including juvenile-onset/adult-onset, ketosis-prone/non-ketosis-prone, and insulin-dependent/

non-insulin-dependent. All of these names imply phenotypic features that are problematic for categorizing the type of diabetes in individual patients, and consequently, the preferred nomenclature is now type 1 diabetes and type 2 diabetes. Gestational diabetes applies to diabetes

diagnosed during pregnancy. Secondary or other specific types of diabetes encompass a large spectrum of specific causes, including monogenic defects of beta cell function, genetic defects in insulin action or structure, pancreatic diseases such as pancreatitis and hemochromatosis, endocrinopathies, drug/chemical and surgically induced, infections, and uncommon immune-mediated and other genetic syndromes sometimes associated with diabetes. Detailed discussions of each type of diabetes are provided in Section I *Spectrum of Diabetes*, Chapters 2–7.

TYPE 1 DIABETES

Type 1 diabetes represents approximately 5% of all diabetes (1). Central to the pathophysiology of most cases of type 1 diabetes is an autoimmune attack on the pancreatic beta cells resulting in severe insulin deficiency. Although the beta cell damage and death are primarily T cell-mediated, B cell-formed autoantibodies to islet antigens are used as markers of the disease and may play a pathogenic role. Research studies frequently require positivity for one or more of these autoantibodies for the diagnosis of type 1 diabetes. There also may be nonimmune-mediated causes of beta cell damage and destruction and, especially in Asians, a disease called fulminant diabetes has been described (7).

At the time of diagnosis, type 1 diabetes patients are typically of peripubertal age, Caucasian, lean, and with a short duration of symptoms, such as polyuria, polydipsia, and weight loss. A family history of type 1 diabetes is often absent, although a family history of other autoimmune disease, such as Grave's disease or Hashimoto's thyroiditis, may be present. No single clinical characteristic, such as age at diagnosis, body mass, or even ketoacidosis, is sufficiently sensitive and specific for type 1 diabetes to be very useful in distinguishing one form of diabetes from another. For example, with the increasing epidemic of childhood and adolescent obesity, children with type 1 diabetes reflect the usual distribution of weight in their age group. In type 1 diabetes prevention and natural history

studies in which subjects at high risk for type 1 diabetes are followed very closely, over 50% of cases are diagnosed with hyperglycemia that is asymptomatic since the glucose levels are not high enough to cause symptoms, such as polyuria and weight loss (8,9). This is very different than the seemingly abrupt onset of symptoms when people are diagnosed in the clinical setting.

Although severe insulin deficiency is a central element of type 1 diabetes, it may not discriminate between type 1 diabetes, especially early in its course, and type 2 diabetes, especially late in its course. Insulin and C-peptide levels may not be severely low early in the type 1 disease process and during the "honeymoon period," a time shortly after diabetes diagnosis when diabetes appears to go away for a period of a few months to a year. Conversely, some patients with type 2 diabetes may have severe insulin deficiency with very low insulin and C-peptide levels later in its course that overlap the levels in type 1 diabetes. The best laboratory tests to differentiate type 1 from type 2 diabetes are autoantibodies to glutamic acid decarboxylase (GAD), insulin, insulinoma-associated protein 2 (IA-2), and zinc transporter 8 (ZnT8), especially when patients are positive for more than one and have relatively high titers.

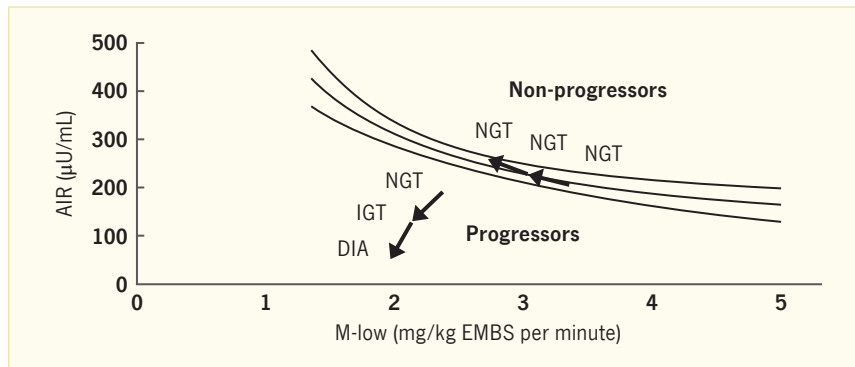
Type 1 diabetes is heterogeneous in a number of respects. Although several genes predisposing to and protecting from type 1 diabetes are well described, genotypes of individual patients span a large spectrum. Many environmental factors may trigger and/or influence the severity of the autoimmune attack on the beta cells, and the specific immune mechanisms operative in individual patients appear to be variable. At diagnosis, patients span the spectrum from severe insulin deficiency with marked hyperglycemia and ketoacidosis to asymptomatic, mild postprandial hyperglycemia. The rate of decline in beta cell function prior to and after diagnosis of type 1 diabetes is also extremely variable. In Caucasians with type 1 diabetes, endogenous beta cell

function declines over months to years with the decline being slower in patients who develop diabetes at an older age (10). More sensitive assays for C-peptide have detected measurable levels after many years of type 1 diabetes (11,12,13). Circulating C-peptide has even been described in Joslin Medalists who have had type 1 diabetes for more than 50 years (14). Over their lifetimes with type 1 diabetes, the frequency of end-organ complications, although definitely affected by glycemic control, is still extremely variable among patients.

The ADA recognizes two forms of type 1 diabetes, type 1a and type 1b diabetes (6). If antibodies are present along with insulinopenia and ketosis, a diagnosis of autoimmune type 1 diabetes or type 1a diabetes may be given. If individuals have a clinical picture consistent with type 1 diabetes, but no antibodies are present, the ADA recognizes a category labeled type 1b diabetes (or idiopathic type 1 diabetes). These latter patients may have a different underlying pathology of disease, or they may have autoantibodies that are not measured by common assays. The use of the term "type 1 diabetes" in *Diabetes in America, 3rd edition*, refers to the autoimmune form (type 1a) unless otherwise specified.

TYPE 2 DIABETES

Type 2 diabetes is the other major type of diabetes and comprises 90%–95% of the total cases of diabetes in the United States and worldwide (1). It is caused by the combination of insulin resistance, largely due to obesity, and deficient insulin secretion, which appears to be the rate-limiting step in type 2 diabetes pathogenesis. Insulin secretion is insufficient given the degree of insulin resistance and is termed relative insulin deficiency. The cause of the insulin secretory defect is probably multifactorial but is usually considered to be metabolic and not autoimmune. Studies of the development of type 2 diabetes in Native American Pima Indians show marked, progressive loss of insulin secretion with progression from normal to impaired glucose tolerance (IGT) to diabetes (Figure 1.1) (15).

FIGURE 1.1. Development of Type 2 Diabetes in Native American Pima Indians

Changes in AIR (insulin secretion) relative to changes in M-low (insulin sensitivity) in 11 Pima Indian subjects in whom glucose tolerance deteriorated from normal (NGT) to impaired (IGT) to diabetic (DIA) (progressors) and in 23 subjects who retained NGT (nonprogressors). The lines represent the prediction line and the lower and upper limits of the 95% confidence interval of the regression between AIR and M-low as derived from a reference population of 277 Native American Pima Indians with NGT. EMBS, estimated metabolic body size.

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A diagnosis of type 2 diabetes assumes the patient does not have any of the causes of diabetes included under secondary or other specific types of diabetes.

Classic clinical characteristics of type 2 diabetes are obesity, onset in middle to late age, positive family history for type 2 diabetes in first degree relatives, and slowly progressive hyperglycemia that is often only minimally symptomatic. Unlike type 1 diabetes, which is most common in Caucasians of northern European origin, type 2 diabetes is more common in minorities, such as African Americans, Hispanics, Asians, and Native Americans, compared to Caucasians. However, as in type 1 diabetes, no clinical characteristics are sensitive and specific for type 2 diabetes. No nonglycemic laboratory tests are specific for type 2 diabetes, except potentially the absence of the autoimmune markers characteristic of type 1 diabetes (see previous section, *Type 1 Diabetes*).

Similar to type 1 diabetes, type 2 diabetes is extremely heterogeneous. It can occur in children and adolescents, as well as in adults, and in lean and obese people; patients span the spectrum from being asymptomatic to presenting with ketoacidosis or nonketotic hyperosmolar coma; and over patients' lifetimes, the frequency of diabetic complications is extremely variable. Diabetic microvascular complications (retinopathy, nephropathy) and neuropathy are qualitatively similar in type 1 diabetes and type 2 diabetes, with

diabetes duration and levels of glycemia playing major roles in their development. Both types of diabetes increase the risk of atherosclerotic macrovascular complications, with the greater age of most patients with type 2 diabetes contributing to absolute risk.

GESTATIONAL DIABETES

Gestational diabetes, as the name implies, refers to diabetes diagnosed during pregnancy. It affects between 3% and 9% of all pregnancies, but can affect more depending on the study and criteria used, as described in detail in Chapter 4 *Gestational Diabetes*. Because perinatal complications can be minimized by aggressive treatment of gestational diabetes, screening during pregnancy is highly recommended. In most cases, the onset of diabetes during pregnancy is caused by insufficient insulin secretion to compensate for the marked increase in insulin resistance that occurs with pregnancy, especially during the second and third trimesters. Consequently, gestational diabetes commonly resolves or markedly improves after delivery. The development of gestational diabetes identifies these women as having an underlying beta cell lesion, and with time, they have a very high risk (>50%) of developing permanent type 2 diabetes (16).

Occasionally, type 1 diabetes or type 2 diabetes will be diagnosed during pregnancy but not due to the metabolic

changes of pregnancy, and in these cases, the diabetes remains after delivery. By custom, the diagnosis in these patients is termed type 1 diabetes or type 2 diabetes, rather than gestational diabetes. The high prevalence and younger age of onset of type 2 diabetes, concurrent with the epidemic of obesity, has made type 2 diabetes more common in women of childbearing age.

SECONDARY OR OTHER SPECIFIC TYPES OF DIABETES

The fourth category of diabetes is secondary or other specific types of diabetes. The main categories are monogenic defects of beta cell function, genetic defects of insulin action, exocrine pancreatic disease, endocrinopathies, drug/chemical induced, infectious, and uncommon immune-mediated and genetic syndromes associated with diabetes (Table 1.1) (6). Previously, the monogenic defects of beta cell function were referred to as maturity-onset diabetes of youth (MODY). More recently, many of the specific gene defects have been identified and are described as such. For example, MODY1 involves the gene for hepatocyte nuclear factor 4-alpha (HNF4 α) on chromosome 20, and MODY2 involves the glucokinase gene on chromosome 7. This list will likely continue to expand as more specific genetic causes for diabetes are identified. More information about these other types of diabetes is provided in Chapter 6 *Other Specific Types of Diabetes* and Chapter 7 *Monogenic Forms of Diabetes*.

COMBINED TYPE 1 AND 2 DIABETES

Although type 1 and type 2 diabetes are thought to represent distinct and separate disease processes with hyperglycemia as a common denominator, there is no reason why both diseases—or at least some components of each disease—cannot occur together in individual patients. For example, type 1 diabetes does not protect against development of obesity and associated insulin resistance; therefore, in the setting of epidemic obesity, an increasing number of patients with type 1 diabetes may also have features of type 2 diabetes. Conversely, when

TABLE 1.1. Other Specific Types of Diabetes

| | |
|--|---------------------------------|
| A. Genetic defects of beta cell function | |
| 1. MODY3 (Chromosome 12, HNF-1 α) | |
| 2. MODY1 (Chromosome 20, HNF-4 α) | |
| 3. MODY2 (Chromosome 7, glucokinase) | |
| 4. Other very rare forms of MODY (e.g., MODY4: Chromosome 13, insulin promoter factor-1; MODY6: Chromosome 2, NeuroD1; MODY7: Chromosome 9, carboxyl ester lipase) | |
| 5. Transient neonatal diabetes (most commonly ZAC/HYAMI imprinting defect on 6q24) | |
| 6. Permanent neonatal diabetes (most commonly KCNJ11 gene encoding Kir6.2 subunit of beta cell K _{ATP} channel) | |
| 7. Mitochondrial DNA | |
| 8. Others | |
| B. Genetic defects in insulin action | |
| 1. Type A insulin resistance | 4. Lipotrophic diabetes |
| 2. Leprechaunism | 5. Mutant insulins |
| 3. Rabson-Mendenhall syndrome | 6. Others |
| C. Diseases of the exocrine pancreas | |
| 1. Pancreatitis | 5. Hemochromatosis |
| 2. Trauma/pancreatectomy | 6. Fibrocalculus pancreatopathy |
| 3. Neoplasia | 7. Others |
| 4. Cystic fibrosis | |
| D. Endocrinopathies | |
| 1. Acromegaly | 5. Somatostatinoma |
| 2. Cushing's syndrome | 6. Aldosteronoma |
| 3. Glucagonoma | 7. Hyperthyroidism |
| 4. Pheochromocytoma | 8. Others |
| E. Drug or chemical induced | |
| 1. Vacor | 7. β -Adrenergic agonists |
| 2. Pentamidine | 8. Thiazides |
| 3. Nicotinic acid | 9. Dilantin |
| 4. Glucocorticoids | 10. γ -Interferon |
| 5. Thyroid hormone | 11. Others |
| 6. Diazoxide | |
| F. Infections | |
| 1. Congenital rubella | 3. Mumps |
| 2. Cytomegalovirus | 4. Others |
| G. Uncommon forms of immune-mediated diabetes | |
| 1. "Stiff-man" syndrome | 3. Others |
| 2. Anti-insulin receptor antibodies | |
| H. Other genetic syndromes sometimes associated with diabetes | |
| 1. Down syndrome | 7. Laurence-Moon-Biedl syndrome |
| 2. Klinefelter syndrome | 8. Myotonic dystrophy |
| 3. Turner syndrome | 9. Porphyria |
| 4. Wolfram syndrome | 10. Prader-Willi syndrome |
| 5. Friedreich ataxia | 11. Others |
| 6. Huntington chorea | |

HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of youth.

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TABLE 1.2. Names of Autoantibody-Positive, Otherwise Phenotypic Type 2 Diabetes

| | |
|---|---|
| Type 1.5 diabetes | Progressive insulin-dependent diabetes mellitus (PIDDM) |
| Latent autoimmune diabetes of adults (LADA) | Double diabetes |
| Antibody-positive type 2 diabetes | Latent autoimmune diabetes of youth (LADY) |
| Latent type 1 diabetes | Autoimmune diabetes (AID) |
| Slowly progressive IDDM (SPIDDM) | |
| Youth overt diabetes of maturity (YODM) | |

SOURCE: J. Palmer, personal communication

islet cell antibodies were discovered as a marker of the autoimmune process underlying type 1 diabetes, a much higher prevalence of autoantibodies (5%–10%) was found in patients with phenotypic type 2 diabetes than in nondiabetic controls (1%). Widespread testing for GAD autoantibodies identified patients with phenotypic type 2 diabetes as having Latent Autoimmune Diabetes of Adults (LADA). Other names designed to indicate the combination of type 1 diabetes and type 2 diabetes in individual patients, such as double diabetes and type 1.5 diabetes, were introduced. In fact, a large number of names have been used for autoantibody-positive patients with phenotypic type 2 diabetes (Table 1.2). The most consistent characteristic of these patients is that beta cell function declines more rapidly than in autoantibody-negative type 2 diabetes patients, and consequently, autoantibody-positive phenotypic type 2 diabetes patients need insulin treatment earlier (17).

Although the beta cell damage in type 1 diabetes is primarily autoimmune-mediated, it is likely that some of the metabolic causes of beta cell dysfunction operative in type 2 diabetes may also be operative in type 1 diabetes patients. When intensively treated to near-normal A1c levels, some patients with type 1 diabetes develop obesity and the insulin resistance commonly associated with excess body weight. Such patients commonly also develop other components of the metabolic syndrome, which may result in increased risks for macrovascular disease, compared with nonobese type 1 diabetic patients (18).

PREDIABETES

Prediabetes is a term used to define subjects with a high risk of future type 1 diabetes or type 2 diabetes, with the understanding that not all subjects who meet the definition for prediabetes will develop diabetes. Prediabetes for type 2 diabetes includes people with elevated, but subdiabetic, fasting glucose levels (called "impaired fasting glucose" or IFG), postprandial glucose intolerance ("impaired glucose tolerance" or IGT),

A1c 5.7%–6.4% (39–46 mmol/mol), and those with a history of gestational diabetes. There is no accepted definition of prediabetes for type 1 diabetes, but a combination of genetic, immune, and metabolic markers can be used to accurately assess risk of future type 1 diabetes (19). The use of such information to estimate risk of future type 1 diabetes has been validated and successfully used in type 1 diabetes prevention trials (9,20,21).

PROBLEMS WITH CURRENT CLASSIFICATIONS

There are several problems or limitations with the current classifications of diabetes. The diagnosis of type 1 diabetes versus type 2 diabetes usually depends on phenotypic characteristics that are not specific for either type of diabetes. Ideally, the classification of diabetes should be based on pathoetiology, rather than being descriptive. In type 1 diabetes, the presence of autoantibodies to GAD, insulin, IA-2, and ZnT8 supports an underlying

autoimmune etiology. With this in mind, it might be appropriate to divide diabetes into autoimmune versus nonautoimmune diabetes. On the other hand, absolute insulin deficiency has specific clinical implications and may be a useful way of categorizing the disease, as was done in the past with the terms “insulin-dependent” versus “non-insulin-dependent” diabetes. Unfortunately, no markers are specific for type 2 diabetes; using the absence of the markers for autoimmune diabetes as a diagnostic criterion for type 2 diabetes is a major problem.

Type 1 and type 2 diabetes are not mutually exclusive. Many patients may have both diseases or at least some components of both disease processes. For example, the frequency of autoantibodies to islet antigens is much higher than expected in obese children with phenotypic type 2 diabetes (22). Furthermore, the characteristics of type 1 and type 2 diabetes in individual patients may vary over time. For example, obesity can

develop in lean patients initially classified with type 1 diabetes, or islet autoantibodies may occur in phenotypic type 2 diabetes patients who were previously autoantibody negative (23).

Finally, the role of autoimmunity, detected by autoantibodies, may not be the same for type 1 versus type 2 diabetes. Autoimmunity is likely the primary cause of the beta cell lesion of type 1 diabetes; whereas in type 2 diabetes, other mechanisms, such as oxidative stress, islet amyloid polypeptide toxicity, and glucotoxicity, may initiate the beta cell lesion. This damage may then secondarily lead to beta cell autoimmunity, which accelerates the beta cell damage.

The field may be approaching the time when the classification of most cases of diabetes as either type 1 or type 2 needs to be re-evaluated. The epidemic of obesity has hastened the need to rethink the definition of diabetes as type 1 versus type 2.

DIAGNOSIS OF AND SCREENING FOR DIABETES

Diabetes is a complex metabolic disorder, the prevalence of which is rising in the United States (24,25), associated with increased prevalence of obesity (26), vulnerable minorities, and aging (27) in the setting of polygenic risk (28). While the annual incidence in the United States appears to have peaked and has fallen in recent years (2), the epidemic and its risk factors have occurred worldwide (3,4). Carbohydrate metabolism is most obviously deranged and is the basis for biochemical tests of the diagnosis; however, fat metabolism is also adversely affected, and abnormalities in protein metabolism, though more subtle, also exist. For example, fasting free fatty acid and triglyceride levels are elevated, and tissue uptake of amino acids, especially branch chain amino acids, in response to insulin is impaired.

As a “dis-ease,” the derangements in carbohydrate metabolism are clinically recognizable by patients when plasma glucose elevations reach levels that

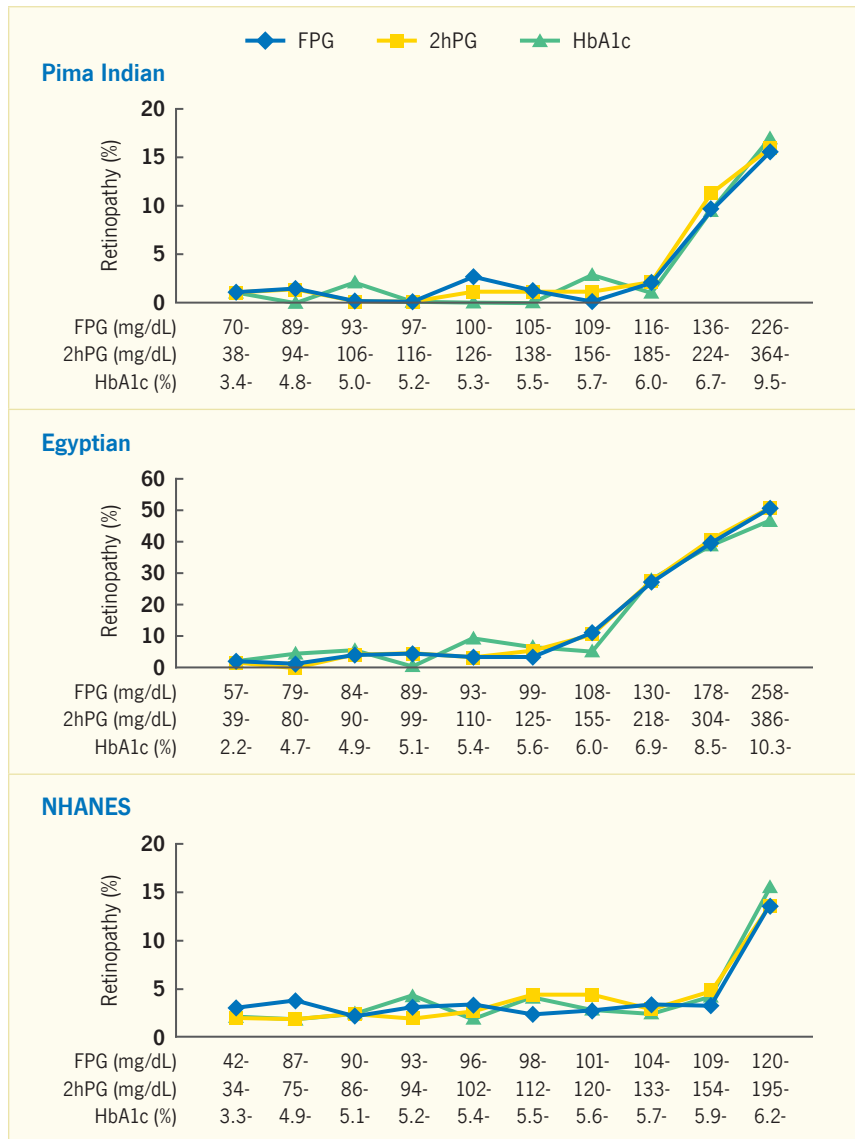
cause glycosuria and polyuria with resultant polydipsia. These symptoms may not occur in type 2 diabetes owing to the slow, progressive rise in glycemia over time; when symptoms are present, they generally are relieved readily by nutritional and pharmacologic therapy. However, the degree of residual hyperglycemia, if chronic, causes the later development of “diabetic complications,” the morbidity and mortality of which dominate the clinical picture and fate of diabetic individuals. These complications also account for a large portion of the economic costs of diabetes in the United States, which amounted to \$245 billion in 2012 (5).

The recognition that hyperglycemia is associated with these complications (29,30,31,32) has placed a premium on glucose-based diagnostic tests with cutpoints that predict an increased risk of retinopathy, the most specific of the diabetic complications (Figure 1.2) (33), although the risks of nephropathy,

neuropathy, and cardiovascular disease (CVD) are also closely associated with and caused, at least in part, by hyperglycemia. While evidence of early specific diabetic tissue damage resulting from microvascular changes might be more definitive than glycemic levels that statistically predict the presence or future appearance of such tissue damage, these tests (e.g., fundus photography) are more cumbersome, more expensive, and/or time-consuming for widespread use. A search for reliable, sensitive, specific, and practical diabetic biomarkers remains a priority.

The diagnostic cutpoints for three glycemia tests recommended by the ADA and an IEC are presented in Table 1.3. The World Health Organization cutpoints differ in that the high risk for diabetes category is defined as fasting plasma glucose (FPG) 110–125 mg/dL (6.11–6.94 mmol/L) and that a random plasma glucose \geq 200 mg/dL does not require symptoms for a diagnosis of diabetes.

FIGURE 1.2. Association of Retinopathy With Various Glycemia Tests in Three Populations: Pima Indian, Egyptian, U.S. NHANES



Retinopathy was determined by ophthalmoscopy in the Pima Indian and Egyptian studies and by fundus photography in the NHANES. Conversions for glucose and HbA1c values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose after 75 g of oral glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; NHANES, National Health and Nutrition Examination Survey.

SOURCE: Reference 33, copyright © 1997 American Diabetes Association, reprinted with permission from The American Diabetes Association

TABLE 1.3. Criteria for Diagnosis of Type 2 Diabetes and High Risk for Type 2 Diabetes

| CRITERIA | TYPE 2 DIABETES | HIGH RISK FOR TYPE 2 DIABETES |
|---|-----------------|-------------------------------|
| A1c | ≥6.5% | 6.0%–6.4%* 5.7%–6.4%† |
| Fasting plasma glucose | ≥126 mg/dL | 100–125 mg/dL‡ |
| 2-hour plasma glucose from an oral glucose tolerance test | ≥200 mg/dL | 140–199 mg/dL§ |
| Random plasma glucose | ≥200 mg/dL | |

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin.

* Recommended by the International Expert Committee 2009.

† Recommended by the American Diabetes Association 2011.

‡ Recommended by the American Diabetes Association 2003.

§ High risk for diabetes by 2-hour plasma glucose was originally called impaired glucose tolerance (IGT) by the National Diabetes Data Group (Ref. 100).

|| With accompanying symptoms of hyperglycemia

SOURCE: References 35, 40, and 102

GLYCATED HEMOGLOBIN

Glycated hemoglobin (A1c) was first considered as a candidate for diagnosis of diabetes by an ADA-constituted committee in 1997, largely based on observational data (33), though it had been previously suggested (34). (The term “glycosylated” hemoglobin has been used interchangeably with “glycated,” but glycated is considered more correct biochemically based on how glucose attaches to hemoglobin. Both terms are used in *Diabetes in America*.) An A1c standard for diagnosis was not adopted for two principal reasons. First and most important, numerous A1c assays using various methods were in wide use with no universally agreed upon relationship among them or standards for reliability and precision. Second, while data were available from which a diagnostic cutpoint could potentially be selected (Figure 1.2), they were relatively sparse and originated from only three small populations.

By 2009, an IEC constituted by the ADA and European Association for the Study of Diabetes judged that the above two impediments had been removed (35). The National Glycohemoglobin Standardization Program (NGSP) (36) had evaluated and standardized the most common A1c assays against the assay employed by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) (Table 1.4) (37,38). This assay had proven stable for ≥20 years with a coefficient of variation (CV) <2% and a coefficient of reliability >98% (39). Moreover, A1c measured by the DCCT assay correlated well with the development of retinopathy, nephropathy, and neuropathy in type 1 diabetes (30). Using a DCCT-aligned A1c assay, a similar correlation with microvascular complications was demonstrated by the United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes (32). Most importantly, the major clinical trials of intensive therapy demonstrated that lowering A1c (using the DCCT-aligned assay) resulted in major salutary effects on microvascular and macrovascular complications (29,30,31,32). A1c targets

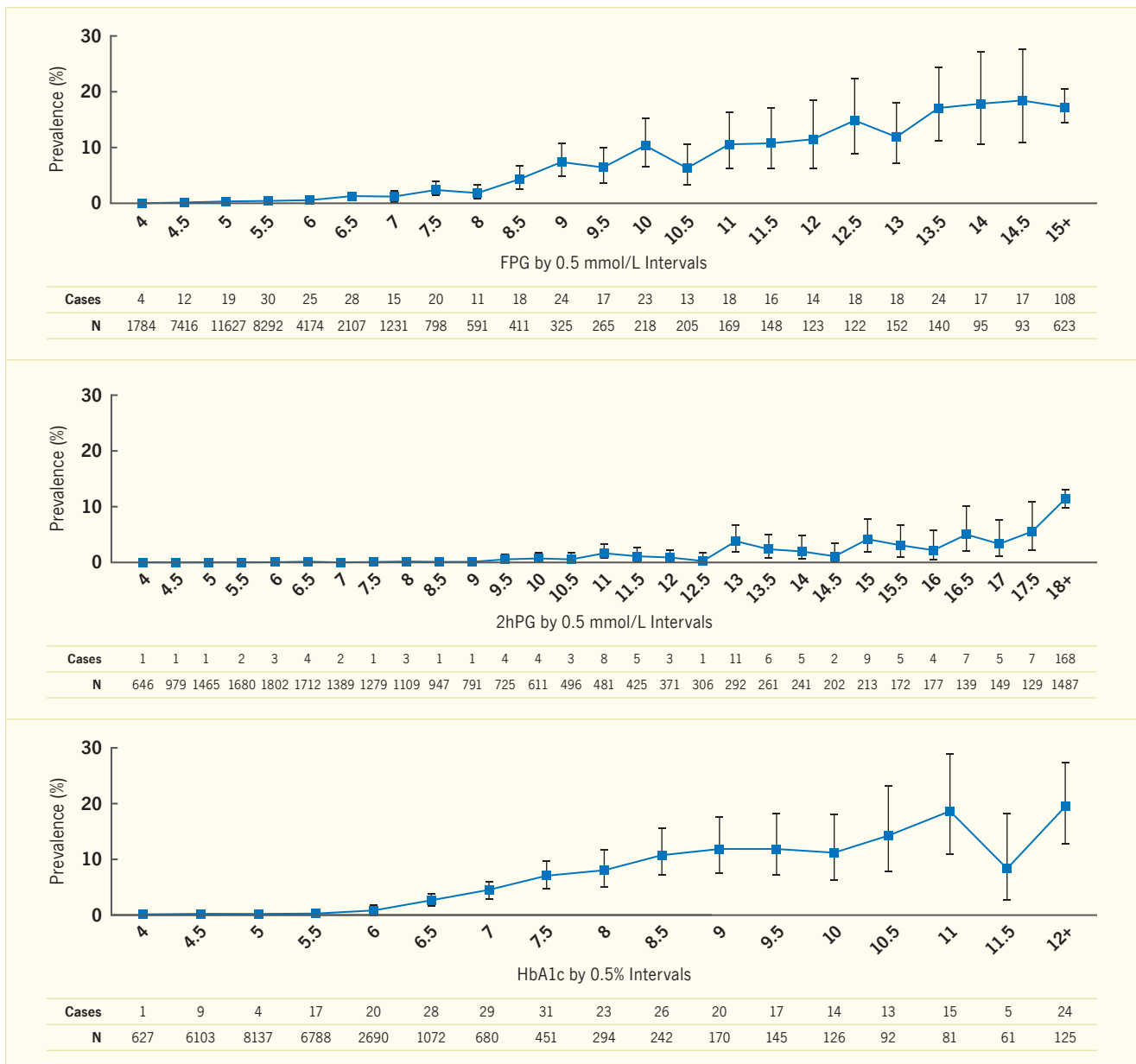
TABLE 1.4. Advantages and Disadvantages of the Most Commonly Used A1c Assays

| ASSAY | MOLECULAR BASIS | ADVANTAGES | DISADVANTAGES |
|-----------------------------|---|---|---|
| Ion exchange chromatography | A1c has lower isoelectric point and migrates faster than other Hb components. | Can inspect chromatograms for Hb variants. Measurements with great precision. | Variable interference from hemoglobinopathies, HbF, and carbamylated Hb, but the current ion exchange assays correct for HbF, and carbamylated Hb does not interfere. |
| Boronate affinity | Glucose binds to m-aminophenylboronic acid. | Minimal interference from hemoglobinopathies, HbF, and carbamylated Hb. | Measures not only glycation of N-terminal valine on β chain, but also β chains glycated at other sites and glycated α chains. |
| Immunoassays | Antibody binds to glucose and between 4 and 10 N-terminal amino acids on β chain. | Not affected by HbE, HbD, or carbamylated Hb. Relatively easy to implement under many different formats. | May be affected by hemoglobinopathies with altered amino acids on binding sites. Some interference with HbF. |

A1c, glycated hemoglobin; Hb, hemoglobin.

SOURCE: Reference 37, © 2011 World Health Organization, reprinted with permission

FIGURE 1.3. Prevalence of Diabetes-Specific Retinopathy According to Glycemic Measurements, DETECT-2 Study, 1982–2004



Data shown are prevalence by fundus photography of moderate or more severe retinopathy with 95% confidence intervals, number of retinopathy cases, and number of participants within each interval by 0.5 unit intervals for FPG (top panel), 2hPG (middle panel), and HbA1c (bottom panel). Conversions for glucose and HbA1c values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

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were accordingly established as critical goals of therapy by the ADA (40) and other diabetes organizations (37).

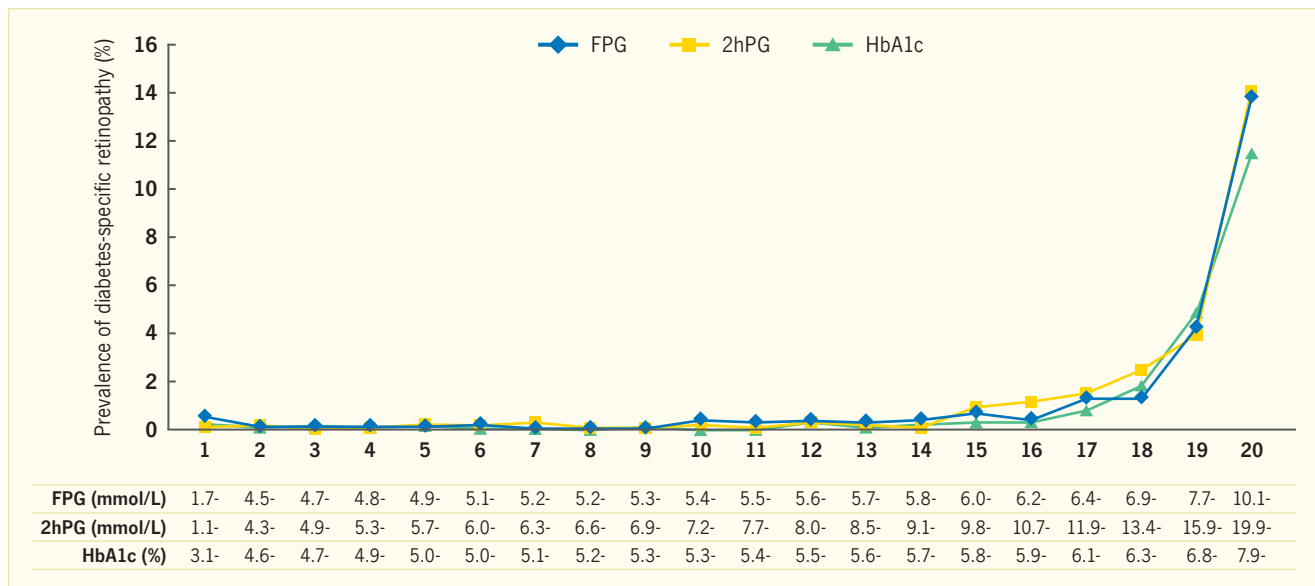
In addition to the standardization and improvements in the A1c assay, the data base comparing the level of A1c to the prevalence of retinopathy had greatly expanded. The DETECT-2 study created a cohort of 44,623 persons age 20–79 years from both sexes representing four studies from the United States, three from Europe, three from Asia, two from Australia, and one from Africa (41). In this cohort, 27,933 subjects had A1c, 41,334 had FPG, and 21,334 had 2-hour plasma glucose (PG) measured with an oral glucose tolerance test (OGTT) by comparable methods. Uniformly graded stereo fundus photographs were collapsed into three categories designated no retinopathy, any retinopathy, and moderate nonproliferative retinopathy (NPDR; Early Treatment Diabetic Retinopathy Study [ETDRS] level ≥ 40) (Figures 1.3 and 1.4). Employing a cutpoint of A1c 6.5%, sensitivity for detection of NPDR was 87.1%, specificity was 85.6%, and positive predictive value was 8.7%. The values compared favorably with those for FPG at 126 mg/dL (76.0%, 86.7%, and

6.6%, respectively) and for 2-hour PG at 200 mg/dL (87.2%, 77.7%, and 4.8%, respectively), the previously established diagnostic glucose levels. A previous report from the Singapore participants in DETECT-2 consisting of >3,000 Malay subjects suggested an A1c cutpoint of 6.6% (49 mmol/mol) with a sensitivity of 87% and a receiver operator characteristic (ROC) area under the curve (AUC) of 0.899 for mild to moderate retinopathy, as well as A1c cutpoints of 6.6%–7.0% (49–53 mmol/mol) for nephropathy and neuropathy with much lower sensitivities (42). In a study of 1,006 persons age ≥ 40 years from the National Health and Nutrition Examination Surveys (NHANES) 2005–2006 cohort, A1c was a somewhat better predictor of the presence of retinopathy than FPG (respective ROC AUCs 0.71 vs. 0.65) (43). The cutpoint of A1c 6.5% was endorsed by the World Health Organization (37). It should be noted that this cutpoint is based on the DCCT A1c assay with a normal 1 standard deviation (SD) range of $4.9\% \pm 0.5\%$ (mean $\pm 2SD = 3.9\%–5.9\%$, 19–41 mmol/mol).

The 2009 IEC went beyond affirming A1c and recommended it be the preferred test (35) based on three more considerations:

(1) Practicality: A1c can be sampled at any convenient time of the day without any preparation and is stable at 37°C. By contrast, FPG and 2-hour PG require overnight fasting, and the latter requires oral ingestion of a glucose load (i.e., OGTT), which a minority of individuals find unpleasant due to nausea. Finally, *in vitro* glucose levels fall hour-by-hour unless special collection methods are used. (2) Biological significance: A1c reflects glycemic exposure over 3 months, hence a diabetic state, whereas FPG and 2-hour PG reflect a diabetic *moment* in time with levels that are influenced by previous diet, exercise performance, and most notably, acute stress, such as trauma. (3) Analytical/statistical characteristics: because of the work of the NGSP, the College of American Pathology (CAP) reported in 2009 that of 3,500 laboratories surveyed, 95% had a CV of <5% in the A1c range of 6.0%–7.0% (42–53 mmol/mol), and the average CV was about 3.5% (44). Moreover, when the NHANES tested 685 study participants on two occasions 2 weeks apart, the intraindividual CV was only 3.6% for A1c compared to 5.7% for FPG and a much greater 16.7% for 2-hour PG, confirming previous evidence of the

FIGURE 1.4. Comparison of Prevalence of Diabetes-Specific Retinopathy According to Various Glycemic Measurements, DETECT-2 Study, 1982–2004



Data shown are prevalence by fundus photography of moderate or more severe diabetic retinopathy by vigintiles of FPG, 2hPG, and HbA1c. Conversions for glucose and HbA1c values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose after 75 g oral glucose; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

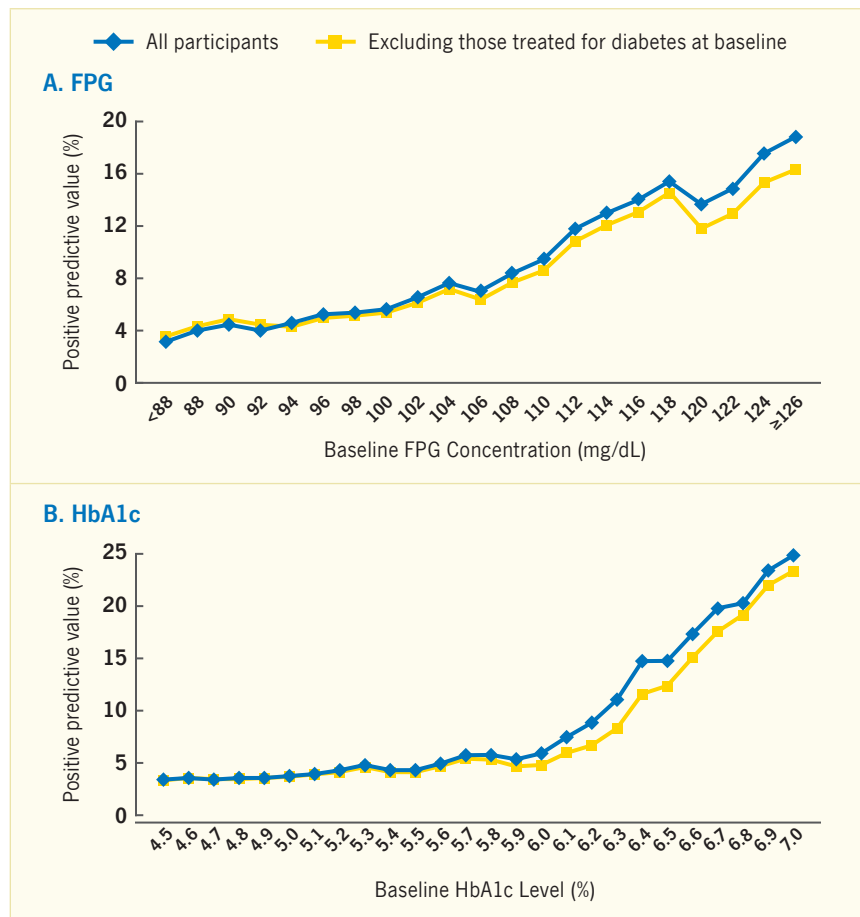
SOURCE: Reference 41, copyright © 2011 American Diabetes Association, reprinted with permission from The American Diabetes Association

poor reproducibility of the OGTT (45). The validity of A1c as a diagnostic test for diabetes is further attested to by its ability to predict the 10-year incidence of the disease diagnosed by retinopathy (Figure 1.5) (46).

Approximately 100 methods for measuring A1c were reported in use in 2011 (47). They can be broadly divided into two groups: those that separate A1c from nonglycated hemoglobin by charge differences, exemplified by cation exchange chromatography, as employed in the DCCT (39); and those that separate glycated from nonglycated hemoglobins by structural differences, such as boronate affinity chromatography and immunoassay (Table 1.4). A1c itself is defined by cation exchange chromatography as adult hemoglobin (HbA) with glucose attached to N-terminal valine of the β chain.

The ADA and the National Academy of Clinical Biochemistry (NCAB) require that A1c assays used for diagnosis should be certified by the NGSP (36). The CAP recommended that by 2013 the limits of accuracy by an external quality assurance program be 6% compared to the target value of a control sample. The NCAB recommends that within-laboratory CV be <2% and between-laboratory CV be <3% for any single A1c method. The accuracy and precision of A1c measurement with point-of-care instruments compared to reference laboratory values is variable, with some investigators reporting satisfactory results (48,49,50,51). Other reports cite insufficient precision or accuracy (52,53), particularly at levels relevant to diagnosis (54), and in individuals with Hemoglobin S (55). Problems include lot-to-lot variations in reagents or instruments (56,57,58), minimal testing of operators' proficiency, and failure to apply laboratory concepts of quality in many point-of-care settings. For example, in one large field evaluation in 1,288 physicians' offices in Norway, a range of 60%–90% met quality criteria (59).

FIGURE 1.5. Positive Predictive Values for the Prevalence of Diabetic Retinopathy 10 Years After Baseline, by Baseline Fasting Plasma Glucose and HbA1c, DESIR Study, 1994–2005



Positive predictive values indicate the percentages of participants with retinopathy if the FPG (panel A) or HbA1c (panel B) level is higher than the indicated value. Retinopathy was assessed by fundus photography using a nonmydriatic digital retinal camera and defined as microaneurysms or worse diabetic retinopathy lesions. Conversions for glucose and HbA1c values are provided in *Diabetes in America Appendix 1 Conversions*. DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome study; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin.

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TABLE 1.5. Factors That Influence A1c and Its Measurement

| FACTORS | INCREASED A1c | DECREASED A1c | VARIABLE A1c |
|-------------------------|--|--|----------------------|
| Erythropoiesis | Iron, vitamin B12 deficiency, decreased erythropoiesis | Administration of erythropoietin, iron, vitamin B12, reticulocytosis, chronic liver disease | |
| Altered hemoglobin | Genetic or chemical alterations in hemoglobin: hemoglobinopathies, HbF, methemoglobin may increase or decrease A1c | | |
| Glycation | Alcoholism, chronic renal failure, decreased intra-erythrocyte pH | Aspirin, vitamins C and E, certain hemoglobinopathies, increased intra-erythrocyte pH | Genetic determinants |
| Erythrocyte destruction | Increased erythrocyte lifespan: splenectomy | Decreased erythrocyte lifespan: hemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs, such as antiretrovirals, ribavirin, and dapsone | |
| Assays | Hyperbilirubinemia, carbamylated hemoglobin, alcoholism, large doses of aspirin, chronic opiate use | Hypertriglyceridemia | Hemoglobinopathies |

A1c, glycated hemoglobin.

SOURCE: Reference 37; and Reference 38, copyright © 2009 John Wiley & Sons, reprinted with permission

Impact of Nonglycemic Factors on A1c

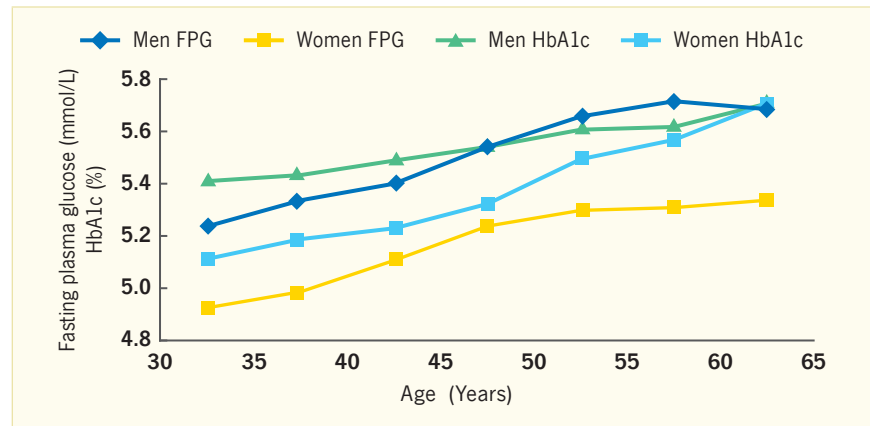
Certain caveats regarding A1c must be highlighted, as it can be influenced by factors other than glycemia (Table 1.5) (37,38). In nondiabetic persons, A1c has been shown to increase with age in multiple cross-sectional studies including: the Framingham Offspring Study, in which an increase of 0.10%–0.14% per decade was observed even after excluding persons with abnormal glucose tolerance based on OGTT (60); the NHANES 2001–2004 (60); a French population of persons age 6–79 years (61); and in the Data from an Epidemiological Study of the Insulin Resistance Syndrome (DESIR) population-based study in western France of persons age 30–65 years at baseline (Figure 1.6) (62). There was a trend toward slightly higher A1c levels in men than women. A similar effect of age and sex on both A1c and FPG was seen; adjustments of A1c for FPG reduced but did not abolish the increase in A1c with age (43).

Genetic influences on A1c have been shown in studies of nondiabetic and diabetic identical twins (63) and in genome-wide association studies (64).

Effects of race/ethnicity, as well as age, on A1c levels are also evident (Figure 1.7), with important differences in the apparent prevalence of diabetes and of the high risk for diabetes (i.e., prediabetes) category (65,66) compared to when these prevalences are determined by FPG or OGTT criteria. In the United States, A1c levels are highest in non-Hispanic blacks, next highest in Mexican Americans, and lowest in non-Hispanic whites, when plotted by age in normal glucose tolerant individuals (Figure 1.7A) and in individuals at high risk for diabetes (Figure 1.7B) (65,66). Non-Hispanic blacks with normal glucose tolerance, prediabetes, or diabetes on OGTT have higher A1c levels than non-Hispanic whites in the Screening for Impaired Glucose Tolerance study and in the NHANES III, apparently independent of a one-time measured glucose level (67).

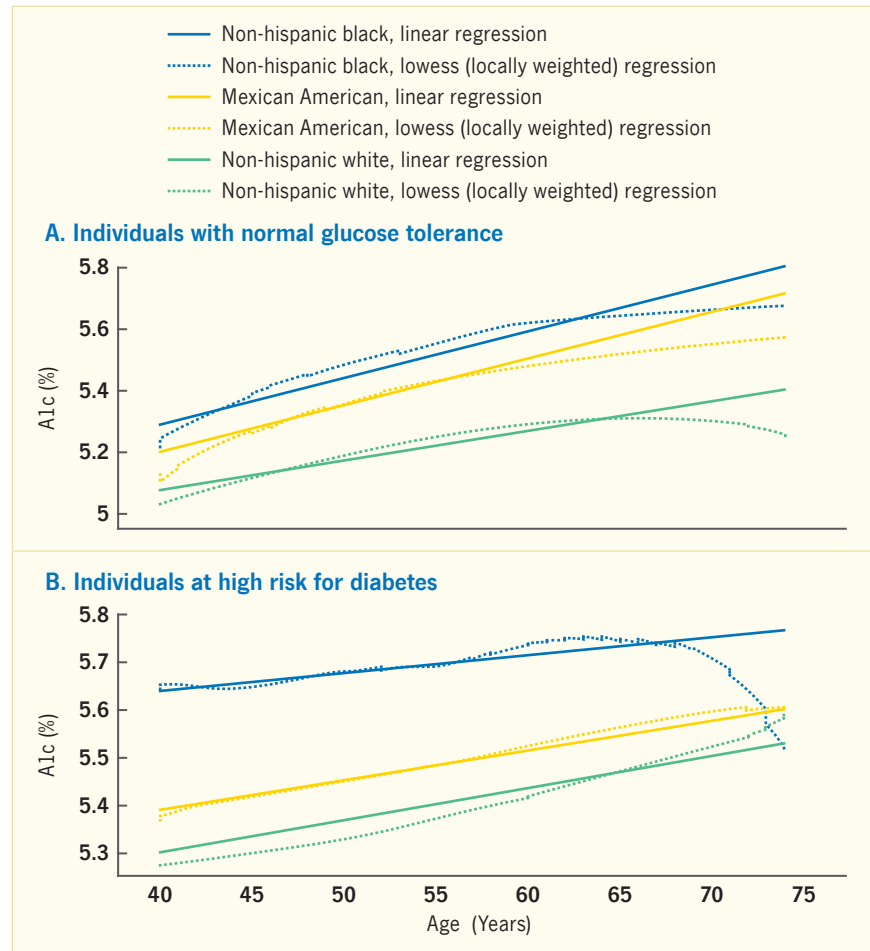
Another study demonstrated parallel rather than equivalent relationships in several different indices of chronic

FIGURE 1.6. HbA1c and Fasting Plasma Glucose, by Age and Sex, DESIR Study, 1994–2005



Conversions for glucose and HbA1c values are provided in *Diabetes in America Appendix 1 Conversions*. DESIR, Data from an Epidemiological Study on the Insulin Resistance Syndrome study; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin. SOURCE: Reference 62, copyright © 2011 American Diabetes Association, reprinted with permission from The American Diabetes Association

FIGURE 1.7. Effect of Age and Race/Ethnicity on A1c Levels, U.S., 1988–1994



Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin. SOURCE: Reference 65, copyright © 2010 Elsevier, reprinted with permission

glycemia compared to A1c in black versus white groups (68), suggesting that chronic glycemia may be truly different among

racies and accurately reflected by A1c levels, rather than a function of disparate relationships between A1c and mean

blood glucose levels. This variation by race/ethnicity is seen in the FPG range >85–124 mg/dL (>4.72–6.88 mmol/L) and in the 2-hour PG range >80–199 mg/dL (>4.44–11.04 mmol/L) (69). When compared to plasma glucose results, A1c cutpoints would overestimate the prevalences of diabetes, IGT, and IFG, particularly in non-Hispanic blacks (65). Interestingly, in a multivariate analysis of the NHANES 2005–2008 cohort, the association of A1c with retinopathy did not differ by race/ethnicity (70). No age-, sex-, or race/ethnicity-specific modifications of diagnostic A1c cutpoints have been advanced to date or organizationally promulgated.

In a Veterans Administration study of almost 300,000 diabetic individuals, average A1c values in summer were 0.22% lower than in winter (71). A similar pattern was observed in a detailed study of 11 diabetic individuals (72). Whether similar variations exist that could affect the diagnosis of diabetes in normal subjects is controversial.

The presence of hemoglobinopathies, such as sickle hemoglobin or hemoglobin C, thalassemias, and others (73), can produce artifactual results in either direction (Table 1.5), depending on the assay employed. An estimated 4% of laboratories participating in a CAP survey in 2010 used A1c methods affected by such abnormalities (74). Although sickle cell disease alone affects 1 in 375 African Americans in the United States (75) and hemoglobin C affects 1 in 50 (73), most methods are either “blind” to such hemoglobinopathies or adjust for them. Nonetheless, it has been recommended that A1c values >15% (140 mmol/mol) be investigated for interference by a hemoglobin variant (44).

Any disease that alters red cell turnover, such as hemolytic anemias or acute bleeding, will affect the A1c level because of shorter red blood cell half-lives and the presence of excess young reticulocytes (76,77). Mild iron deficiency anemia can raise A1c almost 1.0% in some studies (78,79). However, in a NHANES

population of iron-deficient subjects, 30% of whom were anemic, A1c was increased only 0.04% in women and 0.09% in men (80). The presence of iron deficiency increased the risk of A1c \geq 6.5% and the prevalence of diabetes very little. Vitamin B12 deficiency likewise increases A1c, whereas excessive B12 intake decreases A1c. The variable effects of aspirin are dose dependent (81). In a small study in normal individuals, there was enough variability in red blood cell lifespan to account for differences in A1c synthesis (77). A1c cannot be used for diagnosis of gestational diabetes because of altered red cell turnover; pregnant women routinely have lower blood glucose and A1c levels than during their nonpregnant state. Patients with renal failure may also have A1c values that are misleading, especially in the setting of anemia and erythropoietin replacement therapy, rendering A1c assays problematic in patients on chronic dialysis (82). Thus, it is important for practitioners to know which, if any, of these conditions affect A1c results from the laboratory they customarily use.

Although A1c is conventionally thought to express mean plasma glucose (MPG) over the preceding 3 months, a number of reports suggest that within populations, there may be a variable relationship between MPG and A1c (83,84,85,86,87,88,89,90). In these studies, those defined as “high glycaters” have higher A1c levels than would be predicted based on the glucose levels, and those defined as “low glycaters” have lower A1c levels than would have been predicted from their glucose levels. The boundaries of these abnormal glycaters categories are arbitrary. The majority of these analyses have not had frequent enough glucose measurements to know whether MPG has been captured accurately. Fructosamine, a circulating glycosylated molecule reflecting glycemic levels in the previous 2–3 weeks, can be substituted for MPG in such ratios (87). Persistence of low and high glycaters states in particular individuals has also been shown and suggested by its proponents to support its biological significance (86,90). However, a Hemoglobin Glycation Index, one version

of propensity to glycate more or less at a given MPG, does not appear to predict the risk of complications (91,92).

The prevalence of diabetes in the population-based NHANES 2003–2006 (93,94) is shown in Table 1.6. In this study, of the population age \geq 20 years, 12.9% had diabetes, and 39.8% were unaware of it (93). The prevalence of diabetes in those unaware was lowest by the A1c test (1.8%) (94) and highest by the 2-hour PG level from the OGTT (4.9%) (93). Part of this difference in the NHANES report may reflect the fact that A1c and glucose data were not collected in the same years. However, similar differences have been shown in other U.S. studies. The prevalence of diabetes was greatest in those age \geq 65 years and greater in non-Hispanic blacks and Mexican Americans than in non-Hispanic whites by A1c, as well as FPG and 2-hour PG (93,94).

Drawbacks of A1c

As a test for diabetes, A1c has been considered unsatisfactory by some investigators, mainly because of low sensitivity, as seen in Table 1.6, when compared with plasma glucose measurements. For example, in one report, the data were combined from NHANES III, NHANES 2005–2006, and a hospital employee and community population in the Atlanta, Georgia, area (95). All 4,706 subjects had OGTT and A1c measured. With IEC cutpoints of \geq 6.5% for diabetes and <6.0% for normal glucose, A1c was 97% specific but only 30% sensitive compared to the OGTT result. These types of analyses assume that one measure of glycemia represents the gold standard, which is far from clear. In particular, whether a single OGTT with its relatively low reproducibility should be considered a gold standard for the presence of the disease, against which to compare A1c, is debatable. In fact, as noted above, A1c, perhaps because it represents chronic ambient glycemia, rather than the result of an acute and poorly reproducible stress test, appears to capture risk for long-term complications similar to or better than plasma glucose-based measures. DETECT-2 data (Figures 1.3 and 1.4) do not support the superiority

TABLE 1.6. Crude Prevalence of Diabetes Among Adults Age ≥ 20 Years According to the Glycemia Test Used, by Age, Sex, and Race/Ethnicity, U.S., 2003–2006

| CHARACTERISTICS | PERCENT | | | | | | |
|--------------------|----------------|--------------------------------|--------------------------------------|---|-----------------------------|------------------------------|-------------------------|
| | Total diabetes | Previously diagnosed diabetes* | Undiagnosed diabetes (FPG or 2hPG)†‡ | Proportion of total diabetes that was undiagnosed | FPG‡ ≥ 126 mg/dL alone | 2hPG‡ ≥ 200 mg/dL alone | A1c§ $\geq 6.5\%$ alone |
| Age (years) | | | | | | | |
| ≥ 20 | 12.9 | 7.7 | 5.1 | 39.8 | 2.5 | 4.9 | 1.8 |
| ≥ 65 | 31.6 | 17.0 | 14.6 | 46.2 | 6.6 | 14.3 | 3.5 |
| Sex | | | | | | | |
| Men | 12.4 | 7.2 | 5.2 | 42.0 | 3.3 | 4.9 | 2.1 |
| Women | 13.3 | 8.3 | 5.0 | 37.9 | 1.7 | 4.9 | 1.6 |
| Race/ethnicity | | | | | | | |
| Non-Hispanic white | 12.2 | 6.6 | 5.6 | 46.0 | 2.6 | 5.5 | 1.5 |
| Non-Hispanic black | 17.0 | 12.8 | 4.1 | 24.2 | 3.1 | 3.5 | 2.5 |
| Mexican American | 14.7 | 8.4 | 6.3 | 43.0 | 3.5 | 5.7 | 3.0 |

Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose; A1c, glycated hemoglobin; FPG, fasting plasma glucose.

* Previously diagnosed diabetes is based on self-report.

† Undiagnosed diabetes is based on FPG ≥ 126 mg/dL or 2hPG ≥ 200 mg/dL.

‡ Total diabetes, previously diagnosed diabetes, FPG, and 2hPG data are from 2005–2006 (Ref. 93).

§ A1c data are from 2003–2006 (Ref. 94).

SOURCE: Reference 93, copyright © 2009 American Diabetes Association; and Reference 94, copyright © 2010 American Diabetes Association, both reprinted with permission from The American Diabetes Association

of 2-hour PG over A1c or FPG. A long-term longitudinal follow-up of a NHANES cohort with fundus photographs taken at suitable time points is needed to compare the accuracy of the three glycemic tests for diagnosing diabetes in the United States.

Although A1c as a test for diabetes has been endorsed by the ADA and World Health Organization, its acceptance has not been universal (96,97,98,99). The reasons for caution that are cited usually include the drawbacks discussed above, as well as lack of high-quality, affordable assays in some parts of the world.

PLASMA GLUCOSE MEASUREMENTS

In 1979, the National Diabetes Data Group (NDDG) constituted and convened an international committee for the purpose of clarifying the classification of diabetes and systematizing criteria for its diagnosis (100). Prior to this, a variety of glucose cutpoints were used by investigators and employed in physicians' offices. With the exception of two unique small inbred populations with extraordinarily high prevalence and incidence of diabetes, the Pima Indian and Nauruan populations, in whom plasma glucose concentrations were bimodal, the distribution of plasma glucose concentrations were, in

general, unimodal. That is, in the general population, there were not two distinct distributions of glucose measurements separating the diabetic from the nondiabetic persons. This observation required cutpoints for diabetes to be chosen, based on the examples of the two small bimodal populations, as well as statistical considerations, and on agreement by consensus. These originally chosen blood glucose cutpoints were those that predicted progression to "symptomatic diabetes," and in the case of the Pima Indians, to retinopathy and/or nephropathy. The NDDG cutpoints for diabetes were FPG ≥ 140 mg/dL (≥ 7.77 mmol/L) and 2-hour PG ≥ 200 mg/dL after an oral glucose load of 75 g administered in the fasting state (100). This committee also defined a prediabetic high-risk range for diabetes, which they named IGT (Table 1.3), defined as 2-hour PG 140–199 mg/dL after a 75 g OGTT. The ADA and the World Health Organization accepted these recommendations.

In 1997, the ADA constituted another expert committee, composed of American and British diabetologists, which revised the classification and changed the FPG cutpoint for diabetes from 140 mg/dL to 126 mg/dL (33). Importantly, this committee based their recommendations

in part on a strengthened concept from further retinopathy data that the microvascular complications, especially retinopathy, are the disease and elevated glucose levels are biomarkers and likely causal factors. This was based on three studies in different populations (Pima Indian, Egyptian, and a NHANES sample) comparing retinopathy detected by stereo fundus photography with simultaneously measured FPG, 2-hour PG levels after a standard 75 g oral glucose load, and A1c levels. For all three glycemic measures, a sharp inflection in the prevalence of retinopathy was observed at similar deciles in each population with a graded increase in risk at higher glycemic levels (Figure 1.2). The 2-hour PG level of 200 mg/dL was confirmed; however, FPG 126 mg/dL appeared superior to FPG 140 mg/dL for diagnosis of diabetes, in part because it lay partway between a low "background" prevalence of retinopathy and the first sharp rise in these data sets. In addition, certain epidemiologic studies (101) suggested that the lower FPG cutpoint of 126 mg/dL would yield a similar prevalence of diabetes in the population as the 2-hour PG 200 mg/dL cutpoint did. As seen in Table 1.6, however, this has not proven to be the case in the NHANES sample, where prevalence was 2.5% by FPG and 4.9% by 2-hour

PG (93). Nonetheless, 126 mg/dL has remained as the new FPG criterion for diagnosis of diabetes (6). In addition, this committee defined another new category, IFG (analogous to IGT), to recognize individuals whose FPG was above “normal” (≥ 110 mg/dL) but below that of diabetes (< 126 mg/dL) (33). Thus, IFG was initially defined as FPG 110–125 mg/dL.

In 2003, an ADA-constituted follow-up committee redefined IFG as 100–125 mg/dL (5.55–6.94 mmol/L) (Table 1.3) for several reasons (102): (1) It would raise the prevalence of IFG closer to that of the prevalence of IGT in many populations (103); (2) in a ROC analysis of four populations, the optimum sensitivity and specificity for fasting glucose predicting future diabetes ranged from 94 mg/dL (5.22 mmol/L) to 103 mg/dL (5.72 mmol/L); (3) an IFG range of 100–125 mg/dL yielded a similar number of people who develop diabetes in the future as IGT does; and (4) the 95th percentile upper limit of normal for FPG was 106 mg/dL (5.88 mmol/L) (104). FPG and 2-hour PG criteria for diabetes were left unchanged. Random plasma glucose ≥ 200 mg/dL in a person with classic symptoms of diabetes was again deemed sufficient for diagnosis.

Since there is a considerable degree of intraindividual biological variability, compounded by the technical attributes for each assay, confirmation using the same method has been recommended before making the diagnosis of diabetes (35). Using a different test for confirmation will inevitably result in some discordance and resultant uncertainty.

TESTING FOR DIABETES IN THE PEDIATRIC AGE GROUP

In conjunction with a worldwide increase in childhood and teenage obesity, diabetes in youth has increased in prevalence (105,106). The SEARCH for Diabetes in Youth Study reported that the prevalence of type 1 diabetes in U.S. youth age < 20 years rose from 1.48 per 1,000 in 2001 to 1.93 per 1,000 in 2009. The prevalence of type 2 diabetes rose from 0.34 per 1,000 to 0.46 per 1,000 during the same interval (107). A NHANES

report covering survey results from 1999–2010 found prevalences of 0.48% for type 1 diabetes and 0.36% for type 2 diabetes in youth age 12–19 years (108). Minority youth groups appear especially vulnerable to type 2 diabetes, with prevalences of 1.20, 1.06, 0.79, and 0.17 per 1,000 in Native American, black, Hispanic, and white youth, respectively, in 2009 (107). Of additional concern, hypertension, microalbuminuria, and dyslipidemia have been found in adolescents within 2 years of diagnosis of diabetes (109).

In one study of 1,156 urban, multiethnic, obese children and adolescents who received an OGTT and A1c test, 1% had diabetes, and 21% had high risk for diabetes (prediabetes) diagnosed by A1c 5.7%–6.4% (110). The agreement between diagnosis of diabetes by 2-hour PG and A1c was poor (Kappa 0.17). Compared with diabetes diagnosed by 2-hour PG, ROC AUC was 0.81 for A1c $\geq 6.5\%$ and 0.89 for FPG ≥ 126 mg/dL. For A1c, sensitivity was 68% and specificity was 88% compared to OGTT diagnosis, and the optimal diagnostic threshold was A1c 5.8% (40 mmol/mol). For FPG, these values respectively were 83%, 86%, and 102 mg/dL (5.66 mmol/L) (110). In follow-up of a small subcohort at 2 years, A1c and 2-hour PG were the strongest predictors of incident diabetes defined by 2-hour PG. One Pima Indian study suggested that approximately the same baseline glucose cutpoints of FPG (132 mg/dL [7.33 mmol/L]) and 2-hour PG (180 mg/dL [10.00 mmol/L]) predicted an increase in the incidence of retinopathy 20 years later in a group originally diagnosed at age 5–19 years as did the cutpoints in a group originally diagnosed at age 20–34 years (FPG 135 mg/dL [7.49 mmol/L] and 2-hour PG 185 mg/dL [10.27 mmol/L]) (111).

Testing for type 2 diabetes in children is recommended by the ADA (40) if the following criteria are met: (1) body mass index (BMI, kg/m^2) > 85 th percentile, or weight $> 120\%$ of ideal for height; and (2) if any two of the following additional risk factors are present: family history of type 2 diabetes in a first- or second-degree relative, minority race/ethnicity

(African American, Hispanic, Asian American, Pacific Islander, Native American), evidence of insulin resistance (e.g., acanthosis nigricans, hypertension, polycystic ovary syndrome), small for gestational age birth weight, or maternal history of diabetes or gestational diabetes during the gestation of the child. Testing should begin at age 10 years or at onset of puberty, if it occurs before age 10 years. If the initial test is negative, it should be repeated in 3 years (40). Recommendations for diagnostic cutpoints of glycemia are no different than those for adults (112), although more studies have been advocated before use of A1c for testing adolescents is widely adopted, due to the lower sensitivity of A1c (113,114).

In children found to be at increased risk for type 1 diabetes by virtue of positive tests for autoantibodies to islet antigens, regular testing for diabetic glycemia levels is indicated to detect the disease before it manifests clinically, especially as diabetic ketoacidosis. The same cutpoints detailed in Table 1.3 are appropriate.

CYSTIC FIBROSIS-RELATED DIABETES

An estimated 40%–50% of adults with cystic fibrosis now live long enough to develop cystic fibrosis-related diabetes (CFRD) (115), and screening for CFRD is recommended to begin from age 10 years on (116). An annual OGTT is the preferred test, with 2-hour PG ≥ 200 mg/dL considered diagnostic of diabetes. FPG and A1c are considered less satisfactory tests for CFRD (116), although one study suggested that A1c testing is a useful screening tool that effectively reduces the need to perform OGTTs to diagnose CFRD (117).

DISCREPANCIES BETWEEN A1C AND PLASMA GLUCOSE TESTS

In studies of various populations in the United States and around the world, different levels of sensitivity and specificity of the three glycemic tests for diagnosing diabetes have been reported, depending on which test is chosen as the referent. Moreover, even in any given population, the different tests do not always identify the same individuals. A number

of examples are given below to emphasize this difficulty in diagnosing type 2 diabetes, for which there is no biological gold standard.

In a NHANES report covering the U.S. population of adults age ≥ 20 years in 2003–2006, 9.6% had diabetes (7.8% by self-report and 1.8% previously undiagnosed and with A1c $\geq 6.5\%$) (94). In a subsample that also had a FPG and OGTT, 1.2% had undiagnosed diabetes simultaneously by all three methods: A1c, FPG, and 2-hour PG criteria (94). A1c diagnosed 1.6%, FPG diagnosed 2.5%, and 2-hour PG diagnosed 4.9% as having previously undiagnosed diabetes. Compared to 2-hour PG, which detected 90% of the undiagnosed group, A1c detected only 30% of the group (94).

In the Rancho Bernardo Study (118), 85% of those with A1c $\geq 6.5\%$ did *not* meet criteria for diabetes based on FPG and/or 2-hour PG levels, and 33% with diabetes based on plasma glucose levels did not meet the A1c criterion. A1c $\geq 6.5\%$ was 44% sensitive and 79% specific for the diagnosis of diabetes based on plasma glucose measurements (118).

In an independent analysis of the NHANES 1999–2006 cohort (119), 1.8% of adults had both A1c $\geq 6.5\%$ and FPG ≥ 126 mg/dL, concordant for diabetes. However 0.5% of adults had A1c $\geq 6.5\%$ but FPG < 126 mg/dL, while 1.8% had A1c $< 6.5\%$ but FPG ≥ 126 mg/dL, discordant for diabetes. Those with only A1c $\geq 6.5\%$ as evidence for diabetes were more likely to be non-Hispanic black and younger. In the Strong Heart Study of Native Americans (120), A1c $\geq 6.5\%$ identified only 54% of those with FPG ≥ 126 mg/dL, whereas 89% of those with A1c $\geq 6.5\%$ were identified by FPG ≥ 126 mg/dL. Measuring both A1c and FPG in a single blood test would result in a high yield of previously unknown diabetes and high risk for diabetes individuals without the greater inconvenience of an OGTT (121).

In a collaborative analysis of incident diabetes over 5 years in the Australian Diabetes (AusDiab), Inter 99, and DESIR

studies, 21%, 45%, and 75%, respectively, of these cohorts identified as diabetic by the A1c criterion of $\geq 6.5\%$ did *not* meet the FPG criterion of ≥ 126 mg/dL. Likewise, 69%, 63%, and 55%, respectively, of those who met the FPG criterion did *not* meet the A1c criterion (122). However, when each baseline criterion was specifically used for the corresponding diagnosis of incident diabetes, i.e., FPG ≥ 126 mg/dL and/or treatment for diabetes used for baseline FPG, A1c $\geq 6.5\%$ and/or treatment for diabetes used for baseline A1c, the correlations were satisfactory. ROC AUCs for the three cohorts were 0.84, 0.86, and 0.86 for FPG, and 0.91, 0.81, and 0.84 for A1c. Whether the internal consistencies for each test and the discrepancies between them indicate that different forms of diabetes are being predicted or that the tests reflect different stages of diabetes is unclear. Although the A1c assay used in each study was DCCT-standardized, the distributions of A1c within the three population cohorts differed, whereas the distributions of FPG were similar, suggesting another possible reason for their discrepant results.

In an international study of cohorts from six countries and five continents, compared to diabetes diagnosed by OGTT, diagnosis of diabetes by A1c $\geq 6.5\%$ ranged from 17% in Australia to 78% in India (123). Conversely, of those diagnosed with diabetes by A1c $\geq 6.5\%$, diagnosis by OGTT ranged from 27% in Denmark to 98% in Australia. However, in the DECODE study, age- and sex-specific prevalences of undiagnosed diabetes also varied considerably among 13 European cohorts, depending on which plasma glucose measurement—FPG or 2-hour PG—was used to define diabetes (124). Whether methodologic differences underlie the discrepancies between A1c and plasma glucose definitions (or those between FPG and 2-hour PG) (121) or the discordance reflects ethnic differences (123) is uncertain.

The discordance among the three glycemia-based tests in identifying individuals with diabetes is not reflected as much

in their associations with retinopathy, as shown in Figures 1.2 and 1.4. These observations leave clinical practitioners in a quandary as to which test to use in their own settings. This situation is equally problematic for public health authorities interested in conducting screening programs in various locales. Even though the IEC firmly recommended A1c as the preferred test for the reasons given above, in medical communities where minimizing “false negatives” has a high priority and FPG or 2-hour PG are deemed practical, the greater sensitivity of these tests may make them more attractive.

OTHER INDICATORS OF DIABETES

Glycated Albumin

Glycated albumin (GA), an index of the preceding 2–3 week period of glycemia, has been proposed as a diagnostic test for diabetes in Chinese (125) and Japanese (126) studies. In the former, GA correlated strongly with FPG ($r=0.81$) and A1c ($r=0.90$), and a GA cutpoint of 15.7% gave similar results to FPG and A1c on ROC analysis with an AUC of 0.86. (An “ r ” is a measure of correlation of the strength and direction of the relationship between two variables. An r of 1.0 indicates perfect correlation between two variables.) In the latter study, a GA level $\geq 15.5\%$ had a sensitivity of 83% and a specificity of 83% for newly diagnosed diabetes by A1c $\geq 6.5\%$ and/or FPG ≥ 126 mg/dL, while the AUC was 0.91. Although these results appear satisfactory, similar correlation with retinopathy in other populations, availability, and cost will determine whether GA should be considered for the diagnosis of diabetes.

Skin Autofluorescence

Glycation is a universal process in which glucose attaches nonenzymatically to available amino groups on proteins. The A1c level measures glycation of hemoglobin. Other structural and circulating proteins are glycated proportional to the level of glycemia over the lifespan of the particular protein. Subsequent chemical rearrangements can lead to the formation of advanced glycation endproducts (AGEs) with crosslinking.

Autofluorescence of AGEs accumulated in skin collagen consequent to excessive glycemic exposure over time can be measured quantitatively with external devices (127), is associated with the presence of complications (128,129,130), as are AGEs (131), and can indicate the presence of diabetes or IGT. In a study of 351 community subjects, 84 (24%) had abnormal glucose tolerance on OGTT; 65% of these participants had IGT, and 35% had type 2 diabetes. ROC curves showed an AUC of 0.80 for the autofluorescence method versus 0.72 for FPG and 0.80 for A1c against the OGTT diagnosis considered as the gold standard in this study (132). In a study of Dutch subjects with one or more metabolic syndrome criteria, skin autofluorescence was found superior to FPG and noninferior to A1c in the diagnosis of diabetes and IGT (133). In a study of Greek subjects (134), a nonstandard point-of-care device was used to measure A1c and defined diabetes as $\geq 6.5\%$. By comparison, an arbitrarily chosen level of skin autofluorescence was 98% sensitive and 56% specific for diabetes. The skin autofluorescence test yielded ROC AUC of 0.90 for the diagnosis of diabetes. The autofluorescence method, however, was unable to discriminate between women with gestational diabetes and control pregnant women, each at a mean 27 weeks of gestation (135).

While the autofluorescence method for diagnosis of diabetes may hold promise, its widespread use will depend on studies of population-based cohorts, its relationship to the development of diabetic complications, availability and standardization of methods, and its cost-effectiveness compared to glycemic measurements.

Retinopathy

As a complication that can be measured objectively with fundus photography, retinopathy has been used to establish the levels of glycemia that diagnose diabetes. It is considered relatively specific for diabetes. Patients not known to have diabetes who, on routine eye exam with ophthalmoscopy, are observed to have

nonproliferative retinopathy beyond microaneurysms only are likely to have diabetes. A glycemic test should be performed to confirm this impression.

In the Diabetes Prevention Program (DPP), microaneurysms alone have been reported in 6.9% of participants with IGT and FPG 95–125 mg/dL (5.27–6.94 mmol/L) who had not progressed to diabetes, as well as in 10.8% of these subjects who had developed diabetes within the previous 3 years (136). Moreover, in hypertensive and possibly even in normal subjects, microaneurysms have been observed (137,138). In the Beaver Dam Eye Study, 7.1% of nondiabetic subjects at baseline had microaneurysms (139), and the 15-year cumulative incidence of microaneurysms in these subjects was 8.4%. In the Inter 99 Eye Study, 8.3% of nondiabetic subjects had retinopathy not associated with any measure of short-term, long-term, or current glycemia (140). A1c was not significantly different in those with and those without microaneurysms. Thus, microaneurysms are not a 100% specific indicator of diabetes. Nonetheless, normal glucose tolerant persons with retinopathy are at twice the risk of developing diabetes within 5 years as are those without retinopathy (141). Moreover, in various populations, 13% (142), 15% (143), 21% (144), and 37% (145) of patients already have retinopathy at the time their diabetes is diagnosed. Since this phenomenon has been observed exclusively in type 2 diabetes, it probably reflects to some extent delayed diagnosis.

Neuropathy

Peripheral sensorimotor neuropathy is associated with myriad diseases other than diabetes. However, patients without any other obvious explanation for peripheral neuropathy may be found to have diabetes or IGT by OGTT (146,147). Therefore, in the absence of known diabetes, screening patients with neuropathy for diabetes is appropriate. In one series, 20% of 73 such patients had diabetes, and an additional 36% had IGT and/or IFG (147).

Clinical Symptoms

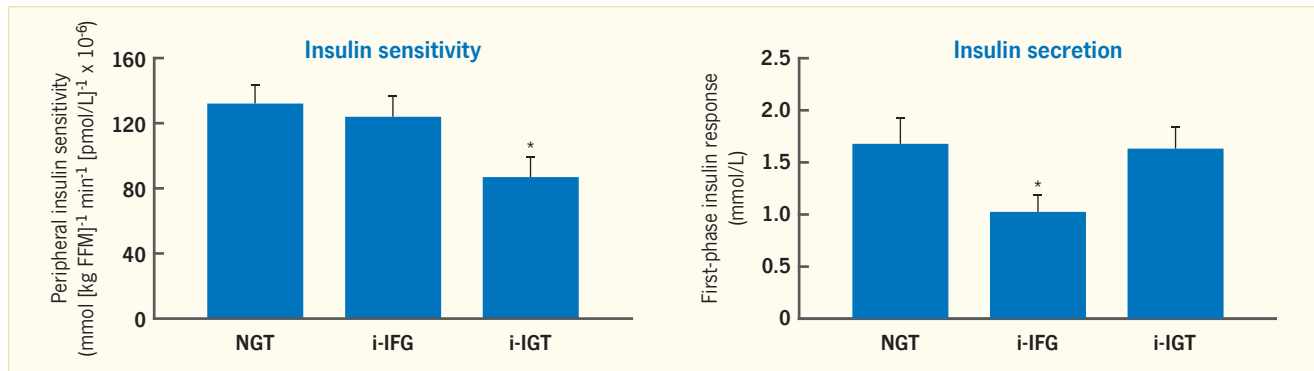
Patients with polyuria, polydipsia, and/or unintentional weight loss are immediately suspect, and a random plasma glucose ≥ 200 mg/dL confirms the diagnosis of diabetes (Table 1.3). Indeed with such a presentation, even a positive test for glycosuria would be diagnostic of diabetes, and urine should be tested for ketones to assess the type.

Genetic Testing

Genome-wide association studies have identified numerous genetic variants associated with type 2 diabetes, most of which have modest effects on the relative odds that an individual will have diabetes (148,149). Some alleles of *TCF7L2*, the most powerful genetic risk factor discovered to date that is widely shared across populations, may increase the risk of diabetes by 30% (150) and progression of IGT to type 2 diabetes by 55% (151). Some genetic variants are associated with the transitions from normal FPG to IFG and from IFG to type 2 diabetes (152). At present, however, genotyping does not improve discrimination of individuals at risk for type 2 diabetes beyond that provided by well-established clinical risk factors (149). More information on genetic associations with type 2 diabetes can be found in Chapter 14 *Genetics of Type 2 Diabetes*.

GLYCEMIC RISK FACTORS FOR DIABETES

IGT and IFG are well-substantiated risk factors for future development of diabetes. They are commonly combined into a single category denoted by the term “prediabetes.” There are several reasons why this usage is unfortunate (153). Most important is the evidence that the risk of diabetes is continuous throughout the normal range of FPG down to at least 80 mg/dL (154) and does not begin at a 2-hour PG level of 140 mg/dL for IGT (155). Thus, these arbitrary categories characterize the regions between the respective cutpoints for diabetes and the upper limits of normal. Second, grouping IGT and IFG together overlooks several important differences between them. The conditions have different prevalences in the U.S. population: IFG 25.7%,

FIGURE 1.8. Insulin Sensitivity and Insulin Secretion in Persons With Impaired Fasting Glucose, Impaired Glucose Tolerance, and Normal Glucose Tolerance

Left panel: insulin sensitivity measured by a euglycemic-hyperinsulinemic clamp. Right panel: insulin secretion measured by first phase insulin response to an intravenous glucose tolerance test. Error bars represent standard errors. FFM, fat-free mass; i-IFG, isolated impaired fasting glucose, n=18; i-IGT, isolated impaired glucose tolerance, n=28; NGT, normal glucose tolerance, n=20.

* p<0.05 compared to NGT

SOURCE: Reference 159, copyright © 2009 Springer, reprinted with permission

IGT 13.8%, and IFG or IGT 29.5% in the age group ≥ 20 years (93). Only a minority of those affected have both conditions, with IFG more common in men and IGT more common in women (103). While IGT and IFG both predict future diabetes, they do not necessarily do so in the same individuals (103). Their pathophysiologies also appear dissimilar, IFG is more likely associated with defective insulin secretion and IGT with insulin resistance (Figure 1.8) (156,157,158,159). Even more subtle differences in insulin secretion have been reported (158). Most studies, but not all, report IGT to be a stronger predictor of progression to diabetes than IFG. In a meta-analysis of studies from 1979 to 2004, the relative risks for incident diabetes were 6.35 with IGT, 4.66 with IFG (110–125 mg/dL), and 12.13 with both IGT and IFG (160). These progression rates are all predicated on the specific values chosen to define each prediabetic state. Choosing different levels would almost certainly give different results. Moreover, 2-hour PG is a stronger predictor of CVD and total mortality than FPG (161). Finally, the term prediabetes suggests an inevitable progression to diabetes, when as many as 39% of IGT individuals return to normal glucose tolerance spontaneously on a repeat test 2–6 weeks later (162).

On the other hand, retaining IGT and IFG as particular but separate risk categories takes advantage of the large backlog

of informative epidemiologic studies employing them, some of which are ongoing. Using the term prediabetes may have some public health benefits if it facilitates public education about diabetes and increases the number of people who modify their lifestyle appropriately, but this theoretical benefit needs to be tested. Should public screening for diabetes become justified, the term prediabetes could also help target high-risk individuals and encourage them to undergo screening.

In any case, IGT, IFG, and the combined state IGT/IFG are considered separately as risk factors, along with A1c, in the

following sections. Prediabetes is not considered as a single entity in this section dealing with high risk for diabetes.

Prevalences of High-Risk Glycemic States

The prevalences of IGT and IFG along with that of the A1c category defined as “high risk” in the NHANES 2003–2006 cohort are shown in Table 1.7 (93,94). The prevalences of all high-risk categories varied markedly in all age, sex, and race/ethnicity subgroups. In another NHANES report on the 2005–2008 cohort age ≥ 18 years, the prevalences of IGT (13.7%), IFG 100–125 mg/dL (26.2%), IFG 110–125 mg/dL (7.0%), and A1c 5.7%–6.4% (14.2%) varied

TABLE 1.7. Crude Prevalence of High Risk for Diabetes Among Adults Age ≥ 20 Years According to the Glycemia Test Used, by Age, Sex, and Race/Ethnicity, U.S., 2003–2006

| CHARACTERISTICS | PERCENT | | | |
|--------------------|-------------|------|------|------|
| | IGT or IFG* | IGT* | IFG* | A1c† |
| Age (years) | | | | |
| ≥ 20 | 29.5 | 13.8 | 25.7 | 3.4 |
| ≥ 65 | 40.4 | 26.9 | 36.6 | 8.1 |
| Sex | | | | |
| Men | 36.0 | 14.6 | 32.1 | 3.6 |
| Women | 23.4 | 13.1 | 19.8 | 3.2 |
| Race/ethnicity | | | | |
| Non-Hispanic white | 29.3 | 14.5 | 25.8 | 2.7 |
| Non-Hispanic black | 25.1 | 10.0 | 20.5 | 7.2 |
| Mexican American | 31.7 | 13.0 | 26.8 | 3.6 |

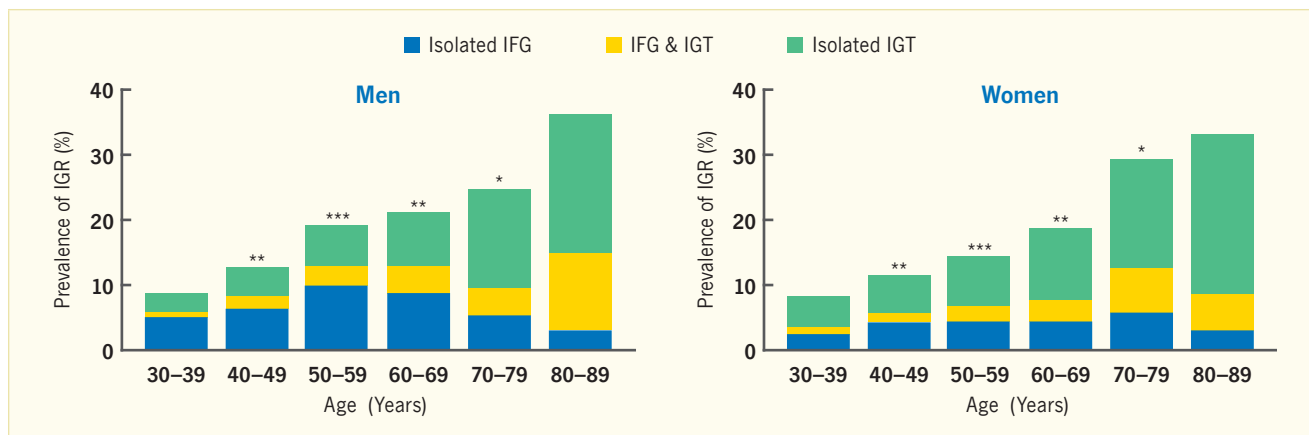
Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

* IFG is defined as fasting plasma glucose 100–125 mg/dL; IGT is defined as 2-hour plasma glucose 140–199 mg/dL. IFG and IGT data are from 2005–2006 (Ref. 93).

† High risk for diabetes is defined as A1c 6.0%–6.4%. A1c data are from 2003–2006 (Ref. 94).

SOURCE: Reference 93, copyright © 2009 American Diabetes Association; and Reference 94, copyright © 2010 American Diabetes Association, both reprinted with permission from The American Diabetes Association

FIGURE 1.9. Age- and Sex-Specific Prevalences of High-Risk Characteristics for Diabetes, DECODE Study, 1981–1997



Data are combined from 15,606 persons in 13 European cohorts from the DECODE Study. Isolated IFG is defined as FPG 110–125 mg/dL and 2hPG <140 mg/dL. Isolated IGT is defined as FPG <110 mg/dL and 2hPG 140–199 mg/dL. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. 2hPG, 2-hour plasma glucose; DECODE, Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGR, impaired glucose regulation; IGT, impaired glucose tolerance.
 *p<0.05 **p<0.01 ***p<0.001

SOURCE: Reference 124, copyright © 2003 American Diabetes Association, reprinted with permission from The American Diabetes Association

considerably (163). Among the group with IGT, 58% had IFG 100–125 mg/dL, 23.4% had IFG 110–125 mg/dL, and 32.3% had A1c 5.7%–6.4%. To what extent these discordances (which depend on the cutoffs selected) have a biologic basis and might indicate the need for differences in preventive therapy remains to be determined, but they do not support the concept of a single state defined as prediabetes. Moreover, secular trends in the prevalence of high-risk diabetes differ depending on which test is used to define this state (164). From 1999 to 2010, among adults age ≥18 years, the prevalence of A1c 5.7%–<6.5% increased from 10.3% to 19.3% (an 87% increase), whereas the prevalence of IFG increased from 25.4% to 27.5% (only an 8% increase) (164). For comparison, the prevalences of isolated IFG (110–125 mg/dL), isolated

IGT, and the combined groups in Europe are shown in Figure 1.9 (124). Both in the United States and in Europe, IGT is the most prevalent of these conditions, particularly in older adults.

Impaired Glucose Tolerance

In 1979, the NDDG recognized a category of abnormal glycemia for which they recommended the term “impaired glucose tolerance” or IGT. This category defined individuals whose 2-hour PG values on an OGTT were 140–199 mg/dL, just below the diabetes cutpoint and just above the level of people who were not at any apparent risk for developing diabetes during long-term follow-up. Lending importance to a diagnosis of IGT is that such individuals have increased rates of CVD (as do subjects with IFG) (165) and proteinuria (166) on follow-up, even in the absence of diabetes development (166).

Table 1.8 shows the rates of progression from IGT to diabetes in various populations and follow-up periods (167). The crude percentage of persons with IGT progressing to diabetes ranged from 23% to 62%, and the incidence ranged from 3.6% to 8.7% per year (overall 5.7% per year). BMI was an independent risk factor for progression in all populations, and higher rates were seen in minority groups (167). Some of the variation in rates of progression might have been accounted for by differences in follow-up time (6–15 years), in variations in the intervals at which outcomes were assessed (from 1 to 8 years), and in definitions of diabetes diagnosis (FPG ≥140 mg/dL, 2-hour PG ≥200 mg/dL, physician diagnosis, or self-reported use of hypoglycemic medication). However, consistently higher rates were seen in the Hispanic, Mexican American, Native American, and Nauruan

TABLE 1.8. Progression from Impaired Glucose Tolerance to Type 2 Diabetes in Various Populations

| POPULATIONS | NUMBER WITH IGT | PERCENT PROGRESSION | PERSON-YEARS OF FOLLOW-UP | INCIDENCE PER 100 PERSON-YEARS |
|---------------------------------------|-----------------|---------------------|---------------------------|--------------------------------|
| Baltimore Longitudinal Study of Aging | 675 | 28% | 5,337 | 3.58 |
| Rancho Bernardo Study | 186 | 26% | 1,227 | 4.00 |
| San Antonio Heart Study | 353 | 30% | 2,463 | 4.34 |
| Nauru Study | 305 | 47% | 2,262 | 6.28 |
| San Luis Valley Diabetes Study | 177 | 23% | 562 | 7.29 |
| Pima Indian Study | 693 | 62% | 4,924 | 8.73 |

IGT, impaired glucose tolerance.

SOURCE: Reference 167

TABLE 1.9. Progression to Type 2 Diabetes From Impaired Fasting Glucose Versus Normal Glucose Tolerance

| YEARS (REF.) | COUNTRY | NUMBER OF PERSONS (AGE) | FOLLOW-UP (YEARS) | OR (95% CI) IFG 100–125 mg/dL | OR (95% CI) IFG 110–125 mg/dL |
|-----------------|----------------|-------------------------|-------------------|-------------------------------|-------------------------------|
| 2000–2002 (183) | United States | 1,667 | 7.8 | 2.9 (2.2–3.6) | |
| 1989–1991 (184) | United States | 6,753 | 7.5 | 13.2 (10.8–16.2) | |
| 1993–1997 (185) | United Kingdom | 1,040 (40–69 years) | 10 | 4.1 (1.9–8.7) | 6.9 (3.1–15.2) |
| 2000–2002 (186) | Germany | 6,803 (50–74 years) | 5 | 4.7 (3.7–6.0) | |
| 1990 (187) | Italy | 837 | 10 | | 11.0 (5.6–21.9) |
| 1998–1999 (188) | Spain | 630 | 6 | | 8.4 (3.1–23) |
| 1998–2006 (189) | Japan | 10,042 | 5.5 | 7.4 (4.7–11.7) | |
| 1997–2003 (190) | Japan | 6,241 | 4.7 | 6.2 (4.3–8.8) | |
| NR (191) | Iran | 5,794 | 6.5 | 8.4 (6.4–10.0) | 9.6 (7.5–12.3) |

The definition of diabetes differed slightly among studies but generally included subject or physician report of treatment for diabetes and fasting plasma glucose ≥ 126 mg/dL. All odds ratios are unadjusted. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. CI, confidence interval; IFG, impaired fasting glucose; NR, not reported; OR, odds ratio.

SOURCE: References are listed within the table.

groups than in non-Hispanic whites. Although categorization of dichotomous high-risk states for diabetes identified groups of individuals that might benefit from prevention, it has been recognized increasingly that the glycemic risk profile is actually a continuum (153).

The high-risk categories acquired greater significance when two trials randomizing individuals with IGT, the DPP in the United States (168) and the Finnish Diabetes Study (169), and one trial randomizing clinics in China (170) to conventional versus intensive lifestyle treatment demonstrated that caloric restriction and regular modest aerobic exercise aimed at weight loss reduced the progression to diabetes by as much as 58% over 3–5 years. The DPP further showed that metformin reduced progression to diabetes by 31% compared to placebo (168). In a short washout period of 11 days, 75% of this metformin effect remained (171). Diabetes was detected and confirmed within 6 months of its onset by regularly measured fasting and OGTT glucose levels. The DPP lifestyle program has been successfully translated into community practice (172). Reductions in the progression to diabetes have also been shown with alpha glucosidase inhibitors after a 3-month washout (173), thiazolidinedione drugs (174,175), sulfonylureas (176), and basal insulin (177). Whether any finite and limited period of drug treatment would result in prevention of or long-term delay in the development of diabetes is unclear (178).

Not all patients with IGT progress to diabetes, and 39% can revert to normal glucose tolerance 2–6 weeks later (162). In the DPP, the frequency of regression from IGT to normal glucose tolerance was increased twofold by intensive lifestyle treatment compared with placebo (179).

Other studies have focused on the 1-hour PG during an OGTT as an even better indicator of future risk for diabetes (180,181), especially if a 1-hour cutpoint of 155 mg/dL (8.60 mmol/L) is coupled with the Adult Treatment Panel criteria for the metabolic syndrome (181). The 1-hour PG ROC AUC for predicting diabetes after 5–7 years was 0.84 compared to 0.79 for the 2-hour PG (180). However, intraindividual variability in two OGTTs performed 48 hours apart was slightly greater for the 1-hour PG than the 2-hour PG (182). If these observations are confirmed in other populations, the 1-hour PG could eventually supplement the 2-hour PG as a “high risk for diabetes” factor.

Impaired Fasting Glucose

The introduction of IFG provided an additional glycemic assessment of risk for developing diabetes that did not require performance of an OGTT. Table 1.9 presents the results of studies in the United States and other countries quantitating the risk of IFG compared to normal glucose tolerance as odds ratios (183,184, 185,186,187,188,189,190,191). The spread was large, ranging from 2.9 to 13.2 in two U.S. studies and from 4.1 to 8.4 in

four other countries using IFG 100–125 mg/dL as the risk factor. A narrower spread from 6.9 to 11.0 was reported with IFG 110–125 mg/dL as the risk factor. The lowering of the bottom of the IFG cutpoint from 110 mg/dL to 100 mg/dL was thought by some to be creating “a pandemic” of diabetes (192). Surprisingly, the average odds ratios were very similar with the two IFG risk factor levels, 9.2 and 9.0, respectively, for IFG 100–125 mg/dL and 110–125 mg/dL. In the one direct comparison of IFG 100–125 mg/dL with IFG 110–125 mg/dL in a U.K. study (Table 1.9), the respective odds ratios were 4.1 and 6.9 (185). Persistence of IFG 100–125 mg/dL on two tests yielded a higher percentage of follow-up diabetes over 5 years (30.4%), than if the second test reverted to normal FPG (5.6%) (193). However, in individuals with normal 2-hour PG on a baseline OGTT, IFG increased the risk of incident diabetes minimally (194). The greater prevalence of the broader definition, which would include more individuals at lower risk of developing diabetes, would lead to an expectation of a lower odds ratio. With greater prevalence and a similar odds ratio, the broader definition of 100–125 mg/dL does yield larger numbers of individuals predicted to develop diabetes and also a larger population that could benefit from preventive measures.

For comparison, Table 1.10 compares the previously defined IFG 110–125 mg/dL to IGT for the percent developing diabetes in follow-up of a number

of populations (103). In the Dutch, Mauritian, and Brazilian-Japanese populations, the risks were quite similar. Among the other countries, the risk of developing diabetes by either test varied greatly. In Native American Pima Indians, the risk was greater with IFG, and the opposite was true in an Italian population. These differences in the predictive power between IGT and IFG for developing diabetes were not unexpected, given the differences in their pathophysiology (Figure 1.8). They may also be affected by ethnic and environmental factors and the fact that the cutpoints are arbitrarily chosen. In community screening programs to identify individuals at high risk for diabetes, the test and cutpoint used will depend on local factors and circumstances.

Glycated Hemoglobin

Somewhat fewer data are available for A1c as a risk factor for incident diabetes. Table 1.11 presents the results from five studies using different A1c levels as risk cutpoints and various A1c levels as referents. The IEC-recommended high-risk range of 6.0%–6.4% yielded the highest odds ratios for development of diabetes in the United States (Figure 1.10) (195), United Kingdom (196), and Italy (197) against different referents. One Japanese study reported an odds ratio for the high-risk range close to but with a slightly lower minimum cutpoint value than the ADA range, i.e., 5.5%–6.4% (37–46 mmol/mol) versus 5.7%–6.4% (189). In another Japanese cohort study, the incidence of diabetes over 4.7 years was 7% in those with A1c 5.7%–6.4% and 9% in those with FPG 100–125 mg/dL (190). The Korean study found A1c more predictive of incident diabetes in females than males (198). The difference in these results likely reflect differences in the populations studied, the glycemic categories employed, the duration of follow-up, and the A1c assays used.

The lower prevalence of high-risk A1c than either IFG or IGT in the United States (Table 1.7) means that its use for screening will yield far fewer individuals who will develop diabetes using OGTT

TABLE 1.10. Comparison of Impaired Fasting Glucose and Impaired Glucose Tolerance as Risk Factors for Developing Type 2 Diabetes in Various Populations

| POPULATIONS | FOLLOW-UP (YEARS) | PERCENT DEVELOPING DIABETES | |
|--------------------|-------------------|-----------------------------|------|
| | | IGT | IFG |
| Dutch | 5.8–6.5 | 33.8 | 33.0 |
| Pima Indian | 5 | 19.9 | 31.0 |
| Mauritian | 5 | 20.8 | 21.6 |
| Italian | 11.5 | 32.5 | 9.1 |
| British | 4.5 | 7.1 | 4.7 |
| Brazilian-Japanese | 7 | 67.6 | 64.3 |
| French | 2.5 | 5.4 | 2.7 |

IFG is based on fasting plasma glucose 110–125 mg/dL; IGT is based on 2-hour plasma glucose 140–199 mg/dL; and type 2 diabetes is based on fasting plasma glucose ≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL. Conversions for glucose values are provided in *Diabetes in America Appendix 1 Conversions*. IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

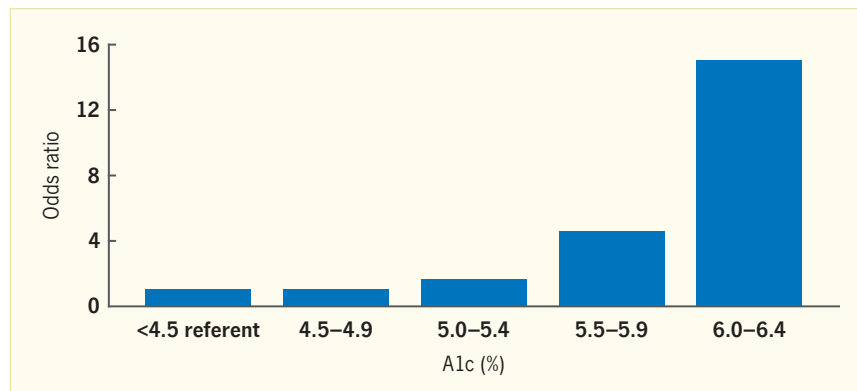
SOURCE: Adapted from Reference 103

TABLE 1.11. A1c as a Risk Factor for Incident Type 2 Diabetes

| YEARS (REF.) | COUNTRY | FOLLOW-UP (YEARS) | REFERENT A1c (%) | HIGH-RISK A1c (%) | ODDS RATIO |
|-----------------|----------------|-------------------|------------------|-------------------|------------------------|
| 2000–2001 (195) | United States | 4.4 | <4.5 | 5.5–6.0 | 4.9 |
| | | | | 6.0–6.4 | 16.0 |
| 1993–1997 (196) | United Kingdom | 3 | <5.0 | 6.0–6.4 | 15.5 |
| 1990 (197) | Italy | 15 | 5.0–5.5 | 5.5–6.0 | 3.8 |
| | | | | 6.0–6.4 | 12.5 |
| 1998–2006 (189) | Japan | 5.5 | <5.5 | 5.5–6.4 | 9.2 |
| 2001–2002 (198) | South Korea | 6 | <5.6 | >5.6 | Men: 3.4 Women: 4.6 |

Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin. SOURCE: References are listed within the table.

FIGURE 1.10. Incidence of Diabetes Over 8 Years, by Baseline A1c, 2000–2008



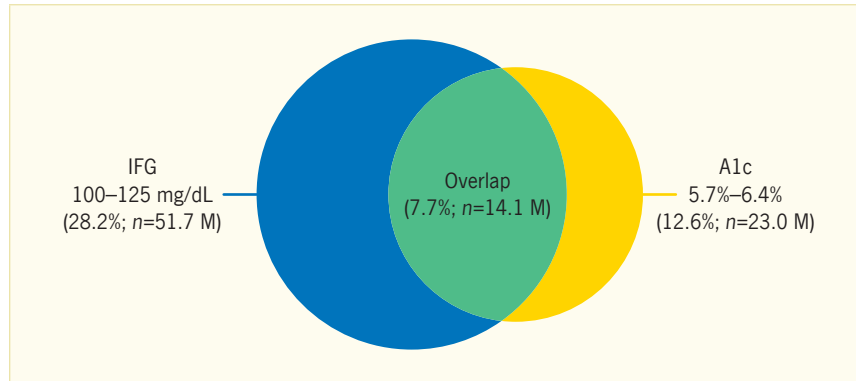
Data from a Veterans Administration study are presented as odds ratios of diabetes incidence versus A1c relative to a referent A1c of <4.5%. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin.

SOURCE: Reference 195

as the gold standard for diagnosis. In a Veterans Administration study of >12,000 persons, the odds ratio for developing diabetes over 8 years of follow-up reached 15 at the IEC A1c level of 6.0%–6.4% (Figure 1.10) (195).

A comparison of the ADA A1c cutpoint of 5.7%–6.4% and IFG 100–125 mg/dL using NHANES 1999–2006 data for prevalence reported that only 7.7% of U.S. adults age ≥20 years had both risk factors, 12.6% had the ADA A1c cutpoint,

FIGURE 1.11. Overlap of Prediabetes Defined by Impaired Fasting Glucose or A1c Among Adults Age ≥ 20 Years Without Diabetes, U.S., 1999–2006



Percentage (%) of high risk for diabetes among U.S. adults age ≥ 20 years by National Health and Nutrition Examination Surveys 1999–2006 data according to IFG 100–125 mg/dL and A1c 5.7%–6.4% criteria for high risk. Conversions for A1c and glucose values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin; IFG, impaired fasting glucose; M, million.

SOURCE: Reference 199, copyright © 2010 American Diabetes Association, reprinted with permission from The American Diabetes Association

and 28.2% had IFG (Figure 1.11) (199). Using IFG as the reference standard, A1c 5.7%–6.4% was 27% sensitive and 93% specific for high risk. Using A1c 6.0% as the cutpoint (IEC), A1c was only 9% sensitive, but 99% specific.

In a review of 16 studies from many countries, the analyzed diabetes incidence using OGTT for diagnosis of diabetes was 0.1% at A1c $< 5.0\%$ (< 31 mmol/mol) and increased to 54% at A1c $\geq 6.1\%$ (≥ 43 mmol/mol). The 5-year incidence of diabetes was $< 9\%$ at A1c

5.0%–5.5% (31–37 mmol/mol), rising to 9%–25% at A1c 5.5%–6.0% and to 25%–50% at A1c 6.0%–6.5% (200). Given its previously noted advantages in diagnosing diabetes, A1c is a viable screening test using the ADA cutpoint of 5.7%–6.4% to enhance its sensitivity for detecting a high risk of diabetes. However, the absence of a gold standard for the diagnosis of diabetes, or demonstrated superiority of one glycemic measure over another in predicting long-term outcomes, makes all of these comparisons difficult to interpret.

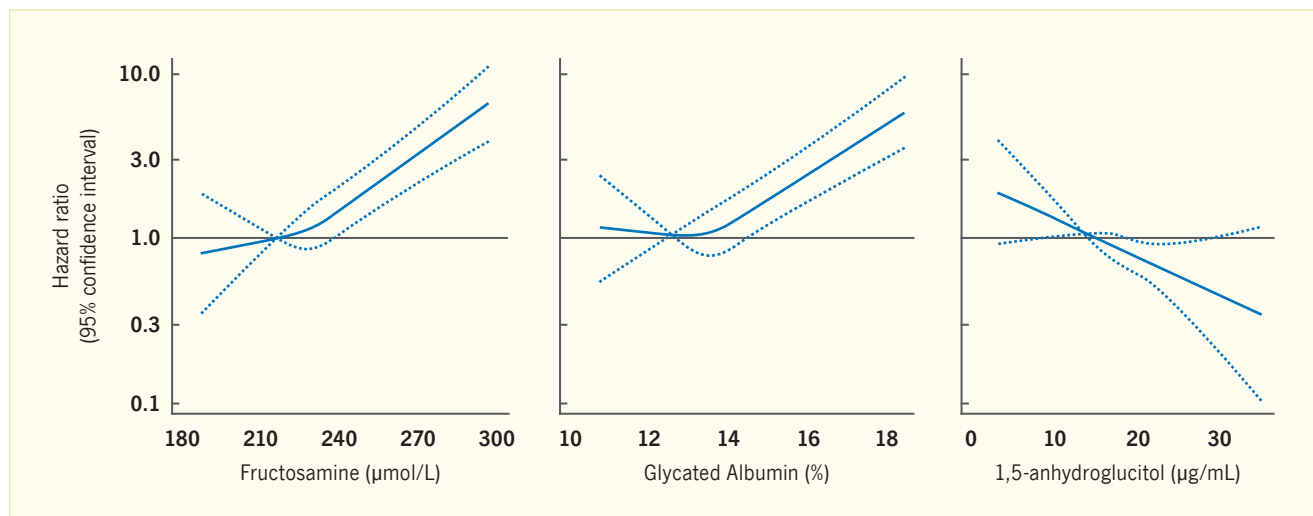
Other Glycemic Risk Factors for Diabetes

In a study conducted in nearly 1,300 participants of the Atherosclerosis Risk in Communities Study (ARIC), GA, fructosamine, and 1,5-anhydroglucitol (1,5-AG) were measured (201). The hazard ratio (HR) for incident diabetes over 3.3 years of follow-up, analyzed as fourth quartile/first quartile, was 5.2 for GA, 4.0 for fructosamine, and 3.7 for 1,5-AG, respectively. (1,5-AG is decreased when plasma glucose rises, especially postprandially). Figure 1.12 shows the relationship of each hazard ratio to the blood level of the marker. Interestingly, all three markers remained significant and substantially unchanged when adjusted for baseline FPG and A1c. Thus, addition of GA or fructosamine to FPG or A1c may improve their strength in predicting incident diabetes.

Combinations of High-Risk Factors

The combination of IGT and IFG in the same individual can greatly increase the risk of developing diabetes. Hazard ratios for this combination as high as 45.6 in Spain (188) over 6 years of follow-up and 20.5 in Italy over 10 years (187) have been reported. By contrast, in the Strong Heart Study of Native Americans, hazard ratios were only 2.9 for IFG 100–125 mg/dL, 4.1 for IGT, and 4.7 for combined IGT/IFG (184).

FIGURE 1.12. Alternative Glycemic Markers and Diabetes Risk



Fructosamine, glycated albumin, and 1,5-anhydroglucitol (1,5-AG). Unadjusted hazard ratios (solid line) for self-reported diagnosed diabetes according to baseline concentrations of glycemic markers from restricted cubic spline models. Dashed lines represent 95% confidence intervals. The models are expressed relating to the 25th percentile with knots at the 25th, 50th, and 75th percentiles. The plots are truncated at the 1st and 99th percentiles. The hazard ratios are shown on a natural log scale.

SOURCE: Reference 201, copyright © 2012 American Diabetes Association, reprinted with permission from The American Diabetes Association

In Germany (186), the combination of A1c 5.7%–6.4% (ADA criterion) plus IFG 100–125 mg/dL yielded a hazard ratio of 10.4, whereas the hazard ratio for isolated A1c was 3.4 and 5.7 for isolated IFG. In a Japanese study of men (202), the ROC AUC for FPG alone was 0.82 and for A1c alone was 0.77, whereas it was 0.85 in a model containing both factors for incident diabetes. In the Strong Heart Study, the hazard ratio of IFG 100–125 mg/dL for FPG-diagnosed diabetes was 3.1, the hazard ratio of A1c 6.0%–6.4% for A1c-diagnosed diabetes was 5.9, and the hazard ratio of A1c 6.0%–6.4% for IFG plus A1c-diagnosed diabetes was only 3.4 (120). Whether it is better to repeat a high-risk result of an A1c test, as recommended by the IEC (35), or combine or follow it with an FPG needs further study.

A diagnosis of high risk for diabetes by combining the results of two tests from the NHANES 2007–2008 cohort has been studied (203). Using A1c 5.7%–6.4%, FPG 100–125 mg/dL, and 2-hour PG 140–199 mg/dL, the concordance between A1c plus FPG and FPG plus 2-hour PG was deemed high, given a sensitivity of 92% and specificity of 84% of the first pair versus the second pair. The first pair also yielded a 24% increased prevalence in non-Hispanic blacks.

SCREENING FOR TYPE 2 DIABETES

Criteria have been proposed to justify screening, but not all have been fulfilled for type 2 diabetes (204,205):

- A. Does diabetes “represent an important health problem that imposes a significant burden on the population”? Unquestionably, the answer is yes. The prevalence of diabetes (24) and the economic costs it generates (5) are on a relentless ascending curve.
- B. Is the natural history of type 2 diabetes understood? Again, the answer is yes. Numerous studies, such as in the Pima Indians (Figure 1.1) (15) and the UKPDS (206), have shown that from the time of clinical diagnosis, a declining capacity of beta cells to secrete enough insulin to compensate

for persistent insulin resistance leads to increasing need for drug therapy to restrain the increasing hyperglycemia and prevent microvascular complications.

- C. Is there a recognizable and detectable early asymptomatic stage when reliable diagnosis is possible? Again, numerous epidemiologic studies have shown that this is so.
- D. Are reliable and generally acceptable tests available to detect early diabetes? FPG and A1c are simple single blood tests; OGTT is less convenient and requires cooperation from the screenee. But, the answer is still yes.
- E. Does treatment started early in an asymptomatic phase provide greater benefit than when treatment is started later, after polyuria and polydipsia appear? The answer to this crucial question is still unknown but may be forthcoming from the Diabetes Prevention Program Outcome Study (DPPOS). As of a 2009 report, the DPPOS has followed 2,665 individuals with IGT for 10 years. Of this cohort, about 700 individuals were diagnosed with diabetes by OGTT when their mean A1c was only 6.0% and the degree and period of glycemic exposure was likely minimal (207). This cohort with good adherence is undergoing regular surveillance for microvascular, neuropathic, and cardiovascular complications. The group originally treated with intensive lifestyle modification for 2.8 years during the DPP continues to maintain the benefit of a reduced incidence of diabetes and modest weight loss (207). This benefit could result in a reduced incidence of diabetic complications.
- F. Are the costs of detecting and treating early diabetes reasonable in the context of total health care expenditures and the available resources and facilities to do so? This question requires local judgment, based on available resources. The DPP and its long-term follow-up have shown that

metformin treatment of its prediabetic cohort was cost-saving, and the life-style intervention was cost-effective.

- G. Can a screening program be maintained in an ongoing pattern rather than as a single one-time effort? This question cannot even be addressed until questions E and F are answered and the benefits and cost-effectiveness of even one sizable public health community screening program are completely assessed.
- H. Are there adverse effects of screening, such as difficulties obtaining health insurance from employers and resultant lower quality of care (208), higher premiums for life insurance (209), or even denial of coverage, job discrimination (210), social stigmatization (211,212), and short-term screenee anxiety (213,214), that could offset the potential benefits of earlier detection of diabetes? Insufficient data on such possible adverse effects are available to provide a firm answer to this worrisome question.

Guidelines for screening by various organizations are given below. The U.S. Preventive Task Force recommendations previously supported screening for diabetes only in individuals with blood pressure $\geq 135/80$ mmHg (215,216) in hopes that early treatment of diabetes will augment the CVD benefit of treating even modest hypertension. This restricted recommendation has been criticized on the grounds that the evidence base used for it was not up to date (217). Furthermore, an analysis of a NHANES 2003–2010 cohort of 7,189 adults demonstrated that a systolic blood pressure of 135 mmHg as a screening criterion yielded a prevalence of undiagnosed diabetes (by A1c or FPG cutpoints) of 4% with a sensitivity of 44% and a specificity of 65% (218). Thus, the usefulness of systolic blood pressure for narrowing the target population that is worth screening is questionable. The U.S. Preventive Task Force now recommends screening for abnormal blood glucose as part of cardiovascular risk assessment in adults age

40–70 years who are overweight or obese (219). The American Academy of Family Physicians recommends screening for diabetes only in adults who have dyslipidemia and hypertension (220); in 2005, the Canadian Task Force on Preventive Health Care made a similar (Grade B) recommendation to prevent CVD and death (221). The Canadian Task Force has since revised their recommendations: the FINDRISC (222) or CANRISK (223) calculators should be administered every 3–5 years to adults, and those found to be at high risk should be screened for diabetes with a A1c cutpoint of 6.5%. Those found to be at very high risk should be screened annually (224). The ADA does not recommend community screening because it may be poorly targeted and positive screenees may not have access to or seek follow-up care (40).

A joint review of the screening issue by the World Health Organization and the International Diabetes Federation in 2003 concluded that “there is no direct evidence as to whether individuals will or will not benefit from the early detection of type 2 diabetes through screening” and noted that “there is an urgent need for direct RCT (randomized clinical trial) evidence” to address the question (225). They also concluded that “opportunistic screening *may* be justified” in health care venues with the capacity to treat those who screened positive for diabetes and to offer preventive measures to those identified to be at increased risk for diabetes. The report acknowledged that screening is going on and urged that health authorities and organizations formulate policies regarding screening, even if not to advocate it.

A Health Technology Assessment (HTA) for the United Kingdom National Screening committee concluded in 2007 (226) that no direct evidence supporting type 2 diabetes screening existed as of then. If targeted screening was undertaken, the first stage should be a questionnaire to narrow the population to those at increased risk. For the second stage, any of the three glycemia tests were considered “acceptable” because

TABLE 1.12. Risk Factors for Type 2 Diabetes

| | |
|--------------------------------------|---|
| BMI ≥ 25 kg/m ² | Polycystic ovaries |
| High-risk ethnicity | Hypertension |
| First-degree relatives with diabetes | History of cardiovascular disease |
| Age ≥ 45 years | HDL cholesterol ≤ 35 mg/dL and/or triglycerides ≥ 250 mg/dL |
| Physical inactivity | |
| Previous gestational diabetes | |

Conversions for cholesterol and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*. BMI, body mass index; HDL, high-density lipoprotein.

SOURCE: Reference 40

each had advantages and disadvantages, but no opinion was rendered by the HTA as to which was “best.”

One study that screened for diabetes has been carried out in a single practice in Ely, U.K. (227,228). In 1990–1992, 1,705 patients were randomly selected to be invited for screening and another 1,705 patients were randomly selected for screening in 2000–2003. Their mortality outcomes were compared to those of 1,526 patients who were never invited for screening. The earlier screened cohort had a borderline significant 21% reduction in total mortality ($p=0.05$) over 10 years compared with the never-screened group, whereas the later screened group had no significant reduction in mortality over 8 years. A systematic review of trials, observational studies, and other reviews conducted for the U.S. Preventive Services Task Force concluded that screening for diabetes did not reduce mortality in the subsequent 10 years. Treatment of screen-detected IGT or IFG did decrease subsequent progression to diabetes (229). It remains to be seen whether a clinical trial with sufficient power that randomizes a much larger number of individuals to be screened for diabetes or not to be screened will be conducted. In the meantime, a community’s public health decision to undertake screening for diabetes will depend on that community’s expected prevalence of diabetes, average age, racial/ethnic mix, available resources, pressure of competing health care needs, and ability to treat positive screenees and to repeat testing of negative screenees. The potential benefit of delaying or preventing diabetes, even if mortality rates are not improved, which is being examined in the DPPPOS, needs also to be considered.

Physicians’ Offices

Opportunistic screening for diabetes in a physician’s office or other health care venue has two important advantages. First, screening can usually readily be targeted to patients at higher than average risk to develop diabetes, thus potentially increasing the yield. The commonly accepted risk factors for diabetes are listed in Table 1.12 (40). These include conditions for which patients are already likely to be receiving care in the office, such as hypertension, and measurements like height and weight easily translated by calculation or nomograms into BMI. In actual practice, however, the results can be unrewarding, with a high cost for each new case identified (230). Clinical factors have also been combined into risk scores, some of which are almost as efficient as using glycemic measurements alone. They improve if glycemic measurements are added. For example, a predictive equation in 1,032 Egyptian subjects used age in years, sex, BMI, systolic blood pressure, high-density lipoprotein (HDL) cholesterol, postprandial time, and random capillary blood glucose (CBG) at that time (231). This equation provided a probability of 0.38 that the subject would have diabetes, IGT, or IFG with a sensitivity of 55%, specificity of 90%, and a positive predictive value of 65%. A risk score created by the ADA for diabetes (232) yielded a sensitivity of 46% and specificity of 60% compared to a random blood glucose of 117 mg/dL (6.49 mmol/L) in a U.K. community (233).

Second, individuals screened positive in a physician’s office are more likely to receive follow-up and appropriate therapeutic intervention, since they are already in the health care system. The cutpoints for a positive screening test are

the same as those for the diagnosis of diabetes itself, with required confirmation by a repeat test. Moreover, those with IGT and IFG or a high-risk A1c level can be identified, depending on the physician's choice of method, and preventive measures instituted.

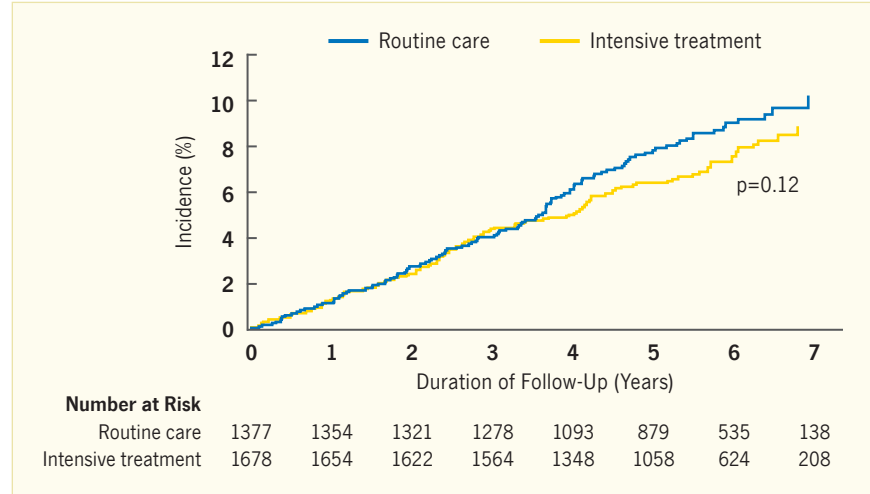
Other Health Care Venues

Another venue for opportunistic screening is hospital emergency departments, with 120 million annual visits in the United States. In one report, a convenience sample of 618 patients presenting to an emergency department was screened by A1c followed by OGTT performed later (234). Mean age was 49.7 years, 52.2% were of minority race/ethnicity, and mean A1c was 5.7%. Compared to diabetes by OGTT criteria, A1c $\geq 6.5\%$ was 54% sensitive and 96% specific. A ROC analysis showed A1c 6.0% to be the "optimum" diagnostic cutpoint yielding a sensitivity of 77% and specificity of 87% with a positive predictive value of 42%. While this was not a random emergency department population-based sample, the results suggest that A1c sampling in the course of an emergency department visit may be reasonable.

In a 2008 Behavioral Risk Factor Surveillance System Survey of 20,618 adults with coronary heart disease (CHD), 31% reported having diabetes and 10% reported having prediabetes (235). Of the 14,335 nondiabetic adults with CHD, 25% reported not having been screened for diabetes in the previous 3 years. The prevalence of diabetes in patients referred for coronary angiography was also increased and opportunistic screening for diabetes was useful in that setting (236). Moreover, diabetic patients with CHD are at increased risk for cardiovascular death (237,238) and deserve intense surveillance and risk factor reduction.

Another high-risk group that could be targeted for opportunistic screening is patients not known to have diabetes who are hospitalized for acute ischemic strokes (239). Using an A1c range of 5.7%–6.4%, 53% of 166 such patients were classified as being at high risk for diabetes, and 15% had newly diagnosed diabetes by A1c $>6.4\%$.

FIGURE 1.13. Cumulative Incidence of Composite Cardiovascular Disease Outcome, ADDITION Trial, 2001–2008



Composite cardiovascular disease includes cardiovascular death, myocardial infarction, stroke, revascularization, and nontraumatic amputation. ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care.

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Screening in dental clinics has been advocated by a Saudi Arabian study (240). Random blood glucose levels ≥ 110 mg/dL were considered a positive screening result (153 of 385 nondiabetic patients tested). Of 128 who had follow-up OGTT, 16% were found to have diabetes, and 16% had IGT and/or IFG (110–126 mg/dL).

Public Screening

Indiscriminate community screening of populations in public locations aims to identify asymptomatic individuals with diabetes who are unaware of their condition.

Possible Benefits of Early Screening for Diabetes

A number of studies have shown that plasma glucose and A1c are continuous risk factors for CVD complications and mortality, including into the subdiabetic range (160,241,242,243,244,245,246,247,248,249). In the ARIC, A1c was a risk factor for mortality in a population without a prior history of diabetes or CVD (250). Compared to a referent A1c of 5.0%– $<5.5\%$, odds ratios for death rose to 1.86, 4.48, and 16.47 in A1c intervals of 5.5%– $<6.0\%$, 6.0%– $<6.5\%$, and $\geq 6.5\%$, respectively (250). Thus, early detection of diabetes by screening might yield a major benefit, if lowering glucose levels resulted in a reduced risk of later CVD

events and mortality. However, neither the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (251,252), Veterans Administration Diabetes Trial (VADT) (253), nor Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) (254) randomized clinical trials were able to demonstrate that intensive treatment that lowered A1c significantly reduced the risk of CVD events. But, in a *post hoc* exploratory analysis, ACCORD reported that intensive treatment did reduce a prespecified composite outcome of ischaemic heart disease (255).

The Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care (ADDITION) has assessed the potential benefits of screening for diabetes, if followed by intensive treatment of newly detected cases (256). ADDITION was a randomized cluster trial using a stepwise screening strategy of risk questionnaires, general practice data plus random blood glucose, FPG, and A1c measurements. A total of 76,308 people screened in 334 general practices yielded 3,057 positive for diabetes. Their 10-year projected risk of CHD was 11% in women and 21% in men using the UKPDS risk engine (257).

The 3,057 positive screenees were subsequently randomized to intensive versus routine care of hyperglycemia, blood pressure, and cholesterol within their primary practices through education of their physicians. Treatment targets were A1c <7.0%, blood pressure <135/85 mmHg, and total cholesterol <5.0 mmol/L (<193 mg/dL) or <4.5 mmol/L (<174 mg/dL) without or with ischemic heart disease, respectively. The cumulative incidence curves for the primary CVD outcome, shown in Figure 1.13, demonstrated no significant benefit in the practices randomized to intensive versus routine care of their screened individuals. At a median 5.3 years of follow-up, the hazard ratio was 0.83 (95% confidence interval [CI] 0.65–1.05) (258). There was also no benefit for any of the individual CVD events (Table 1.13). Institution of intensive treatment likewise did not reduce the prevalence of microvascular outcomes (except possibly severe retinopathy) 5 years later compared to routine care (259).

Moreover, the Cambridge ADDITION group specifically reported the 10-year total and CVD mortality of 15 clinics randomized to intensive treatment after screening and 13 clinics randomized to routine treatment after screening compared to five control clinics where no screening was conducted (260). The hazard ratios for screening versus no screening were 1.06 (95% CI 0.90–1.25) for total mortality and 1.02 (95% CI 0.75–1.38) for CVD mortality.

In the original China Da Qing study of lifestyle treatment of IGT for 6 years, though not a screening study *per se*, there was no difference between the intervention and control groups in CVD events (HR 0.98, 95% CI 0.71–1.37) or all-cause mortality (HR 0.96, 95% CI 0.65–1.41), although the incidence of diabetes was significantly reduced (HR 0.49, 95% CI 0.33–0.73) (170). In a subsequent report of 23 years of follow-up, CVD mortality (HR 0.59, 95% CI 0.36–0.96, $p=0.033$) and all-cause mortality (HR 0.71, 95% CI 0.51–0.99, $p=0.049$) were significantly reduced (261). The long-term observation raises the possibility that detecting IGT in

TABLE 1.13. Cardiovascular Disease Outcomes in the ADDITION Trial of Intensive Versus Routine Care of Patients With Type 2 Diabetes Detected by Screening, 2001–2006

| OUTCOMES | INTENSIVE TREATMENT | ROUTINE CARE | P-VALUE |
|-----------------------|---------------------|--------------|---------|
| Composite CVD outcome | 7.2% | 8.5% | 0.12 |
| Cardiovascular death | 1.5% | 1.6% | NS |
| Myocardial infarction | 1.7% | 2.3% | NS |
| Stroke | 1.3% | 1.4% | NS |
| Revascularization | 2.6% | 3.2% | NS |
| Total mortality | 6.2% | 6.7% | NS |

ADDITION, Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care; CVD, cardiovascular disease; NS, nonsignificant.

SOURCE: Reference 259

a diabetes screening program might yield some benefit if the detected individuals received effective treatment.

A definite clinical advantage to early detection of type 2 diabetes remains to be proven. Community screening as such has not been recommended by the ADA because it may be poorly targeted, individuals screening positive may not seek or have access to appropriate follow-up care, and it has not been proven to be cost-effective (262,263).

Prevalence of Screening

Table 1.14 presents the percentage of individuals who received a fasting blood test for diabetes in the previous 3 years, based on self-reported data from the National Health Interview Survey 2006 (264). The prevalence of previous screening in this population increased with older age, female sex, BMI, and prediabetes, all characteristics that are known to increase the chance of finding diabetes. It is discouraging to see that people of races/ethnicities at higher risk were less likely to be screened, as were people with lesser education, lacking health insurance, and having lower family incomes (Table 1.14). These characteristics define generally underserved communities that might benefit from detection, if followed by effective treatment.

Screening Cutpoints

For opportunistic screening in a physician's office, the cutpoints for a positive screening test are the same as the cutpoints for a diagnosis of diabetes, i.e., A1c $\geq 6.5\%$, FPG ≥ 126 mg/dL, and 2-hour PG ≥ 200 mg/dL (265). However, in the

TABLE 1.14. Prevalence of Having Received a Fasting Blood Test for Diabetes in the Previous 3 Years, U.S., 2006

| CHARACTERISTICS | PERCENT |
|---------------------------------------|---------|
| Age (years) | |
| 20–39 | 21.8 |
| 40–49 | 30.6 |
| 50–59 | 36.7 |
| 60–69 | 42.3 |
| ≥ 70 | 40.0 |
| Sex | |
| Men | 27.8 |
| Women | 32.7 |
| Race/ethnicity | |
| Non-Hispanic white | 32.6 |
| Non-Hispanic black | 29.3 |
| Hispanic | 22.2 |
| Mexican American | 22.6 |
| Non-Hispanic Asian | 20.9 |
| Body mass index (kg/m ²)* | |
| <25 | 24.9 |
| 25–<30 | 30.3 |
| 30–<35 | 39.2 |
| 35–<40 | 41.3 |
| Previous prediabetes* | |
| Yes | 65.7 |
| No | 28.7 |
| Education | |
| <High school | 26.2 |
| High school graduate | 29.1 |
| Some college/Associate's degree | 30.8 |
| \geq Bachelor's degree | 34.5 |
| Health insurance | |
| Yes | 33.3 |
| No | 16.9 |
| Family income | |
| <\$20,000 | 26.6 |
| \$20,000–\$34,999 | 27.1 |
| \$35,000–\$54,999 | 29.4 |
| \$55,000–\$74,999 | 30.9 |
| \geq \$75,000 | 34.8 |

* Body mass index and previous prediabetes data are based on self-report.

SOURCE: Reference 264, copyright © 2014, reprinted with permission from Elsevier

general population, to maximize the yield of asymptomatic diabetic persons, the cutpoint for a positive screen could be set lower than the cutpoint for the diagnosis of diabetes, for example A1c 6.1% or CBG 130 mg/dL (7.22 mmol/L). While higher sensitivity is thereby achieved, it is at the expense of less specificity and more false positives. Referral to a physician's office for confirmation and treatment should always follow. Even a false positive test for diabetes that is not subsequently confirmed by formal testing in a physician's office may have some benefit, as it should alert the individual that, barring a labeling or laboratory error, he/she might be at high risk for future development of diabetes. Moreover, if possible, the screening test should not be burdened by strict conditions and requirements that screenees may forget to adhere to, such as fasting, or be time-consuming, such as a complete, formal OGTT. These considerations favor random blood glucose and A1c measurements for public screening.

The ADA (263) and Canadian Task Force on Preventative Health Care (224) recommend an A1c cutpoint of 6.5% for screening, the same as for diagnosis of diabetes. However, a lower cutpoint of 6.1% yielding a sensitivity of 63% and a specificity of 97% would identify more individuals at risk for diabetes with a relatively low false positive rate (266). There are insufficient data to make a general recommendation for random blood glucose cutpoints.

In a formal test of 1,471 screenees recruited from the community, random CBG with a portable meter was compared to fasting serum glucose (FSG) and 2-hour serum glucose obtained during an OGTT within the subsequent 7 days (2-hour SG) (265). Of the screenees, 10.7% had undiagnosed diabetes as determined by FSG \geq 126 mg/dL and/or 2-hour SG \geq 200 mg/dL. CBG \geq 140 mg/dL was 56%–65% sensitive and 95%–96% specific for diabetes compared to the OGTT criteria. CBG \geq 120 mg/dL (6.66 mmol/L) was 75%–84% sensitive and 86%–90% specific for diabetes. (A 14-point questionnaire [including seven items from

the ADA questionnaire] was 72%–78% sensitive and 50%–51% specific.) The CBG 120 mg/dL cutpoint was considered reasonable (265). It should be noted that fingerstick CBG gives comparable results to plasma and serum glucose, which are themselves nearly identical.

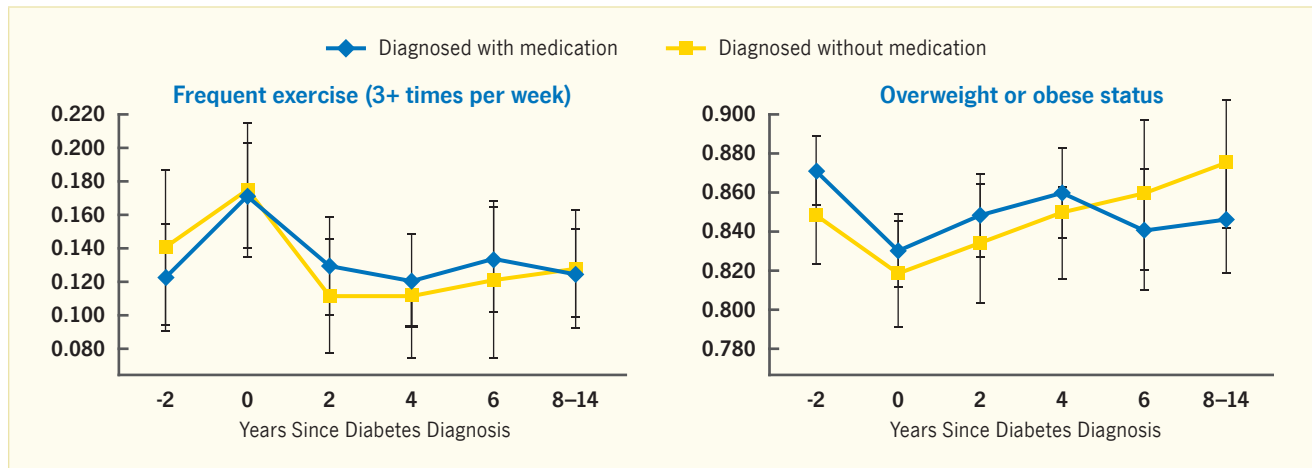
A self-constituted panel published a consensus statement in 2008 focused on A1c and random plasma glucose as screening tests (266). It cited NHANES data (Table 1.7) and recommended A1c 6.1% as a reasonable screening cutpoint, yielding a sensitivity of about 65% and a specificity of 98%, based on FPG \geq 126 mg/dL. A random plasma glucose \geq 130 mg/dL with a similar sensitivity of 63% and a lower specificity of 87%, based on OGTT as “the gold standard” for diagnosis of diabetes, was also recommended, along with FPG \geq 100 mg/dL, as a screening cutpoint. In contrast to the IEC, the panel also recommended that if A1c \geq 6.5% is used as a diagnostic cutpoint for diabetes, that it be confirmed with a plasma glucose test, rather than a repeat A1c test (266).

The use of A1c as a screening test has been supported in screening studies of Native American (267), Hong Kong Chinese (268), and Abu Dhabi (269) populations with and without pairing with FPG. Population-specific optimal cutpoints are described, but generalization to worldwide screening definitions is uncertain. In a study of the NHANES 1988–1994 cohort, compared to FPG \geq 126 mg/dL, A1c 6.1% (two SD above the mean) was 63% sensitive and 97% specific in screening for undiagnosed diabetes (270). In a review of studies of screening to detect diabetes with A1c, 63 studies were identified, of which nine satisfied the criteria for retention in the analysis (271). In addition to ethnicity, age, sex, and prevalence of diabetes were also cited as influencing optimal cutpoints (271). As highlighted before, the decision to embark on public, indiscriminate screening and the procedure(s) to employ in any given community population will likely be an individual one, as will be the results.

Comparison of Screenees Positive by A1c or OGTT

People at high risk for developing type 2 diabetes, or having already developed type 2 diabetes, might have different characteristics depending on which glycemic test is used to identify them. In one study, a group of 844 Italian persons was selected “for their potential risk of type 2 diabetes” for opportunistic screening with both A1c and OGTT (272). There were 317 (38%) at high risk for diabetes by A1c (A1c 5.7%–6.4%) and 351 (42%) by OGTT (2-hour PG 140–199 mg/dL and/or FPG 100–126 mg/dL). Of those with normal glucose tolerance, 17% screened positive for high risk by A1c alone, 21% screened positive by OGTT alone, and 25% screened positive by both tests. FPG, fasting plasma insulin, and Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) were similarly elevated, and the insulinogenic index was similarly lower in all three “at risk” groups compared to those with normal glucose tolerance. CVD risk factors were also similarly abnormal in those at high risk for diabetes by A1c or by OGTT criteria compared to normal glucose tolerance. Thus, in this population, suspected to be at high risk for diabetes by their physicians on clinical grounds, both A1c and OGTT cutpoints (either FPG, 2-hour PG, or both) pointed to individuals with similar metabolic and CVD risk factor characteristics. In a study of Mexican Americans, subjects at high risk for diabetes by either IFG or IGT had distinct reductions in both insulin secretion rates in response to glucose and in insulin sensitivity (158).

Given the insufficient evidence for long-term benefit resulting from community screening and its likelihood of considerable costs, the ADA position to not support community screening cited above seems reasonable. However, physicians should not be precluded from opting to screen their very high-risk patients periodically in the hope that early detection of type 2 diabetes may yet prove to prevent the disease's long-term complications.

FIGURE 1.14. Estimated Probabilities of Health Behaviors and Obesity After Diagnosis of Diabetes

Probability ranges from 0 to 1. For more information, see SOURCE.

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Economic Analysis of Screening

A complete and accurate economic analysis of screening for diabetes is not possible until the long-term benefit and costs of early detection of asymptomatic diabetes are available from actual observation. Projections of models are limited by lack of knowledge of what future costs of care for diabetes and its complications are likely to be. Estimates of the benefits and costs of improved glycemic management and its cost-effectiveness are, however, available from UKPDS (273,274,275), DPP (276,277,278), and even DCCT data extrapolated to type 2 diabetes (279).

According to one model, screening costs depended on the age at which it was started and the frequency at which it was conducted (280). Costs of one quality-adjusted life year (QALY) gained ranged from \$10,500 or less to \$40,778 (280). In another analysis, the cost per QALY gained if screening were targeted to individuals at age 55 years with hypertension was calculated at \$34,375, less than one-tenth the cost of universal screening (281). An analysis of the *direct medical costs* of screening, from a single payer health care system perspective and the societal perspective, of various tests and their cutpoints has also been presented (282).

Because of the wide variability in the results of the economic analyses and the uncertainty of their long-term applicability,

they are not discussed in detail. A randomized controlled trial of screening compared to no screening would be essential as the basis for a realistic assessment of the cost-effectiveness of screening.

Other Health Care Results of Screening

Screening for diabetes or high risk for diabetes (prediabetes) would be beneficial if it was informative to positive screenees and followed by therapeutic or preventive behavior. In one longitudinal study comparing health behaviors over time of individuals before and after diagnosis of diabetes, an approximately 50% increase in physician visits was observed after diagnosis (283). One beneficial effect of receiving a diagnosis of diabetes is a reduction in smoking (283,284). However, neither body weight nor exercise showed beneficial changes after the diagnosis of diabetes, irrespective of medication use (Figure 1.14) (283). This study did not report whether the diagnosis was based on clinical symptoms or screening, although the latter was more likely among those not on medication. In the ADDITION screening study, an intervention to change health behaviors was largely unsuccessful (285), and compared to changing three to four health behaviors, failure to change any health behaviors increased the risk of CVD events in the ensuing 5 years three-fold (286).

In the NHANES 2005–2006 population, only 7.3% of the positive prediabetes screenees were already aware of their condition, so the screening was certainly informative for the large majority of the positives (287). Only 47.7% of those with known prediabetes had been tested for diabetes in the preceding 3 years. When known prediabetic individuals were asked about preventive behavior in the preceding 12 months, about one-half reported efforts at weight reduction or control and a similar percentage reported increasing physical activity. Only about one-third reported being given physician advice to perform these preventive behaviors (287).

SCREENING FOR TYPE 1 DIABETES

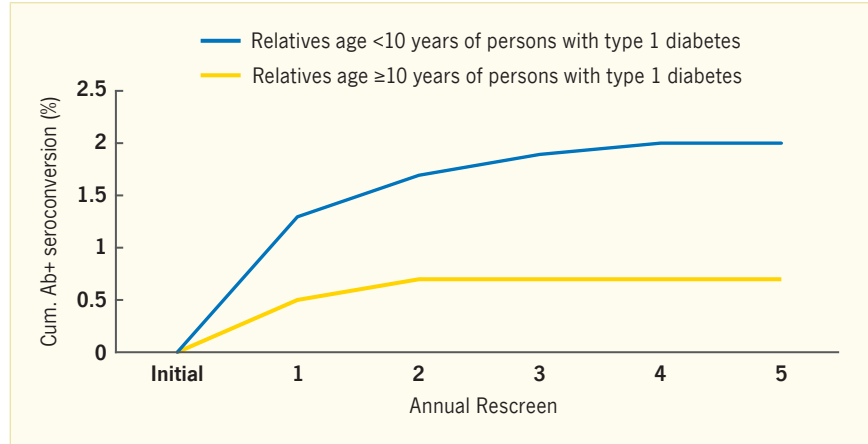
Screening for type 1 diabetes in the general population is not recommended by the ADA on the grounds that relatively few cases would be detected (263). Screening of offspring or siblings (or other relatives) of patients with type 1 diabetes with multiple islet cell autoantibodies, if requested by parents, may be undertaken at the discretion of physicians, or for clinical research purposes. Positive screenees should be counseled about their risk, educated as to symptoms, and monitored periodically for hyperglycemia.

Some idea of the results that can be expected are provided by the TrialNet Natural History Study (288), using research assays not generally available

for clinical use. There were 32,845 first-, second-, or third-degree relatives age 1–17 years who were screened for GAD-65, islet cell antibodies (ICA or ICA-512), and insulin autoantibodies in the course of recruitment for a type 1 diabetes prevention study. Respective cutpoints for those deemed to be autoantibody positive were defined as the threshold indices of ≥ 0.032 , ≥ 0.049 , and ≥ 0.01 . Only 1,807 relatives (5.5%) initially screened positive for any of the three antibodies. Of the 31,038 antibody-negative screenees, 12,365 returned for at least one annual rescreening over 5.8 years of follow-up. Figure 1.15 shows the cumulative incidence of conversion to autoantibody positivity. The rate of conversion was much higher in children age <10 years than in those age ≥ 10 years. The annual incidence of type 1 diabetes was highest in children age 0–4 years (5.4%) and fell in children age 10–14 years (2.9%). The cumulative incidence of conversion to autoantibody positivity appeared to nearly plateau after three to four screenings, suggesting that further testing after 3–4 years may detect few additional at-risk individuals. Two-thirds of all positive screenees were detected on the initial test. A cost/benefit analysis of screening this targeted population for type 1 diabetes, with benefit defined as prevention of diabetic ketoacidosis, remains to be performed.

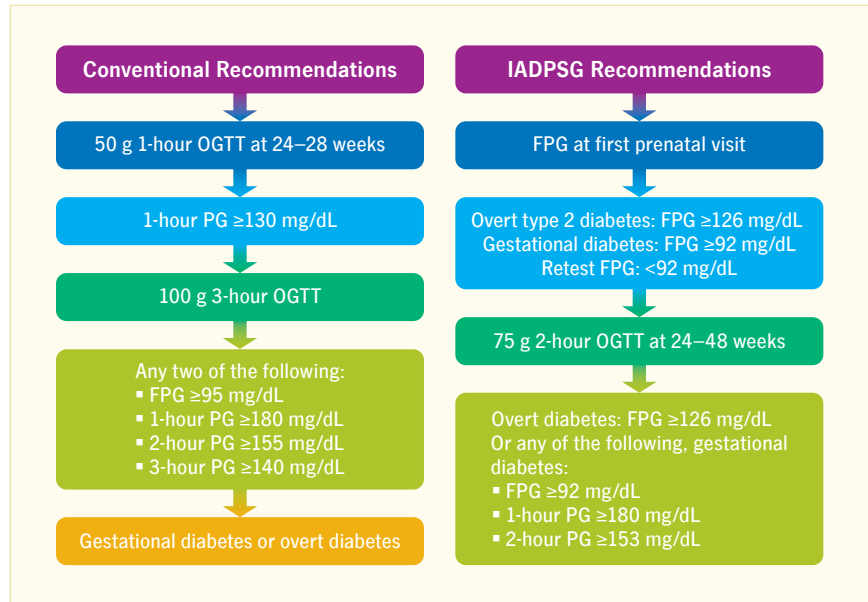
The addition of ZnT8 autoantibodies to the now-traditional other biochemical autoantibodies (i.e., GAD, insulin, IA-2) and ICA improves screening for preclinical type 1 diabetes (289). Moreover, a risk score for the development of diabetes in autoantibody-positive relatives of type 1 diabetic individuals has been constructed from components of age, log BMI, log fasting C-peptide, and the respective sums of glucose and C-peptide levels at 30, 60, 90, and 120 minutes of an OGTT (290). Among relatives whose Diabetes Prevention Trial Risk Score exceeded 9.0, 77%–88% became diabetic within 2 years (290). This compares to 37% identified as dysglycemic (IFG and/or IGT on the baseline OGTT) who developed diabetes within 2 years.

FIGURE 1.15. Development of Islet Autoantibodies on Annual Rescreening of Relatives of Persons With Type 1 Diabetes, TrialNet Natural History Study



SOURCE: Reference 288, copyright © 2011 American Diabetes Association, reprinted with permission from The American Diabetes Association

FIGURE 1.16. Screening Procedures and Cutpoints for Gestational Diabetes and Type 2 Diabetes in Pregnancy



FPG, fasting plasma glucose; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test; PG, plasma glucose.

SOURCE: Adapted from Reference 291

SCREENING FOR GESTATIONAL DIABETES

Gestational diabetes is itself a major risk factor for type 2 diabetes, increasing the later development of diabetes sevenfold (16). Data on gestational diabetes are fully presented and discussed in Chapter 4. A short summary of screening and diagnosis of gestational diabetes is given below for purposes of comparison to the criteria used in the nonpregnant state.

Figure 1.16 (291) presents the criteria for pregnancies at risk for perinatal complications accepted by the American College of Obstetricians and Gynecologists (ACOG) as of 2001, as well as new criteria proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) in 2010. The IADPSG criteria are based largely on the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (292) and have been accepted by the ADA (263). The IADPSG criteria are notable for initiating

detection of gestational diabetes or type 2 diabetes at the first prenatal visit rather than waiting for 24–28 weeks of gestation.

After a positive 50 g OGTT 1-hour PG ≥ 130 mg/dL, the conventional diagnostic cutpoints are any two of the following: FPG ≥ 95 mg/dL, 1-hour PG ≥ 180 mg/dL, 2-hour PG ≥ 155 mg/dL, or 3-hour PG ≥ 140 mg/dL after a 100 g OGTT. The new IADPSG criteria after a 75 g OGTT are any of the following: FPG ≥ 92 mg/dL (5.11 mmol/L), 1-hour PG ≥ 180 mg/dL, or 2-hour PG ≥ 153 mg/dL (8.49 mmol/L). Whether the ACOG or IADPSG test is used, it should be done at 24–28 weeks of gestation, assuming that overt diabetes has not

been found at the first prenatal visit or, in the case of the IADPSG criteria, gestational diabetes at that visit by FPG ≥ 92 mg/dL.

In a Hong Kong Chinese follow-up study of 238 women, 60% of those with gestational diabetes regressed to normal and 6% progressed to diabetes within 1 year postpartum (293). After 4.3 years of follow-up, 20% of participants progressed to diabetes. One year postpartum, IFG (100–125 mg/dL) increased the future incidence of diabetes 3.5-fold (95% CI 1.7–7.0, $p=0.001$) compared to IGT; 29% of those with IFG or IGT or both developed diabetes compared to only 2% of those with normal glucose tolerance.

Application of the IADPSG criteria markedly increases the prevalence of gestational diabetes in the United States to 16% from 2%–5% with the conventional criteria (291). A modeling study has suggested that the use of the new criteria would result in a gain of 1 year of life expectancy, if persistent postpartum diabetes were treated (291). For every 1,000 women screened by the new criteria, 62 QALYs might be gained at a cost of approximately \$1,250,000 (\$20,336 per QALY), provided that postdelivery care reduced the incidence of future diabetes (291).

LIST OF ABBREVIATIONS

| | | | |
|--------------------|---|------------------|--|
| 1,5-AG | 1,5-anhydroglucitol | FSG | fasting serum glucose |
| A1c | glycated hemoglobin | GA | glycated albumin |
| ACCORD | Action to Control Cardiovascular Risk in Diabetes | GAD | glutamic acid decarboxylase |
| ACOG | American College of Obstetricians and Gynecologists | HR | hazard ratio |
| ADA | American Diabetes Association | HTA | Health Technology Assessment |
| ADDITION | Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen Detected Diabetes in Primary Care | IA-2 | insulinoma-associated protein 2 |
| AGE | advanced glycation endproduct | IADPSG | International Association of Diabetes and Pregnancy Study Groups |
| ARIC | Atherosclerosis Risk in Communities study | ICA | islet cell antibodies |
| AUC | area under the curve | IEC | International Expert Committee |
| BMI | body mass index | IFG | impaired fasting glucose |
| CAP | College of American Pathology | IGT | impaired glucose tolerance |
| CBG | capillary blood glucose | MODY | maturity-onset diabetes of youth |
| CFRD | cystic fibrosis-related diabetes | MPG | mean plasma glucose |
| CHD | coronary heart disease | NCAB | National Academy of Clinical Biochemistry |
| CI | confidence interval | NDDG | National Diabetes Data Group |
| CV | coefficient of variation | NGSP | National Glycohemoglobin Standardization Program |
| CVD | cardiovascular disease | NHANES | National Health and Nutrition Examination Survey |
| DCCT | Diabetes Control and Complications Trial | NPDR | nonproliferative diabetic retinopathy |
| DESIR | Data from an Epidemiological Study on the Insulin Resistance Syndrome | OGTT | oral glucose tolerance test |
| DPP | Diabetes Prevention Program | OR | odds ratio |
| DPPOS | Diabetes Prevention Program Outcome Study | PG | plasma glucose |
| EDIC | Epidemiology of Diabetes Interventions and Complications study | QALY | quality-adjusted life year |
| FPG | fasting plasma glucose | ROC | receiver operator characteristics |
| | | SD | standard deviation |
| | | SG | serum glucose |
| | | UKPDS | United Kingdom Prospective Diabetes Study |
| | | ZnT8 | zinc transporter 8 |

CONVERSIONS

Conversions for A1c, cholesterol, glucose, and triglyceride values are provided in *Diabetes in America Appendix 1 Conversions*.

DUALITY OF INTEREST

Drs. Genuth, Palmer, and Nathan reported no conflicts of interest.

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