

CHAPTER 1

CLASSIFICATION AND DIAGNOSIS OF DIABETES

Saul M. Genuth, MD, Jerry P. Palmer, MD, and David M. Nathan, MD

Dr. Saul M. Genuth is a Professor of Medicine, Division of Endocrinology and Metabolism at Case Western Reserve University, Cleveland, OH. Dr. Jerry P. Palmer is a Professor of Medicine, Division of Endocrinology, Metabolism, and Nutrition, and Associate Director of the Diabetes Endocrinology Research Center at the University of Washington/Veterans Affairs Puget Sound Health Care System, Seattle, WA. Dr. David M. Nathan is Director of the Diabetes Center and Clinical Research Center at Massachusetts General Hospital and a Professor of Medicine at Harvard Medical School, Boston, MA.

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 glycated 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 pharmaceutical 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.

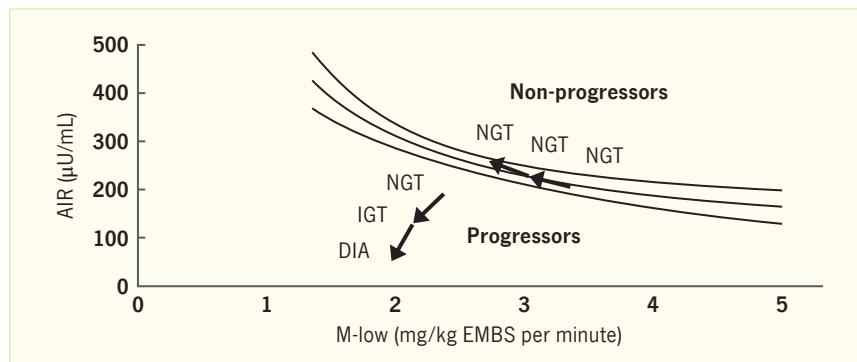
Type 1 diabetes is heterogeneous in a number of respects. Although several genes predisposing to and protecting from type 1 diabetes are well described, genotypes of individual patients span a large spectrum. Many environmental factors may trigger and/or influence the severity of the autoimmune attack 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 measureable 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.

SOURCE: Reference 15, republished with permission of the American Society for Clinical Investigation, copyright © 1999; permission conveyed through Copyright Clearance Center, Inc.

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
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Mutant insulins
6. Others
C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculus pancreatopathy
7. Others
D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Pheochromocytoma
5. Somatostatinoma
6. Aldosteronoma
7. Hyperthyroidism
8. Others
E. Drug or chemical induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β -Adrenergic agonists
8. Thiazides
9. Dilantin
10. γ -Interferon
11. Others
F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Mumps
4. Others
G. Uncommon forms of immune-mediated diabetes
1. "Stiff-man" syndrome
2. Anti-insulin receptor antibodies
3. Others
H. Other genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich ataxia
6. Huntington chorea
7. Laurence-Moon-Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader-Willi syndrome
11. Others

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

SOURCE: Reference 6, copyright © 2013 American Diabetes Association, reprinted with permission from The American Diabetes Association

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

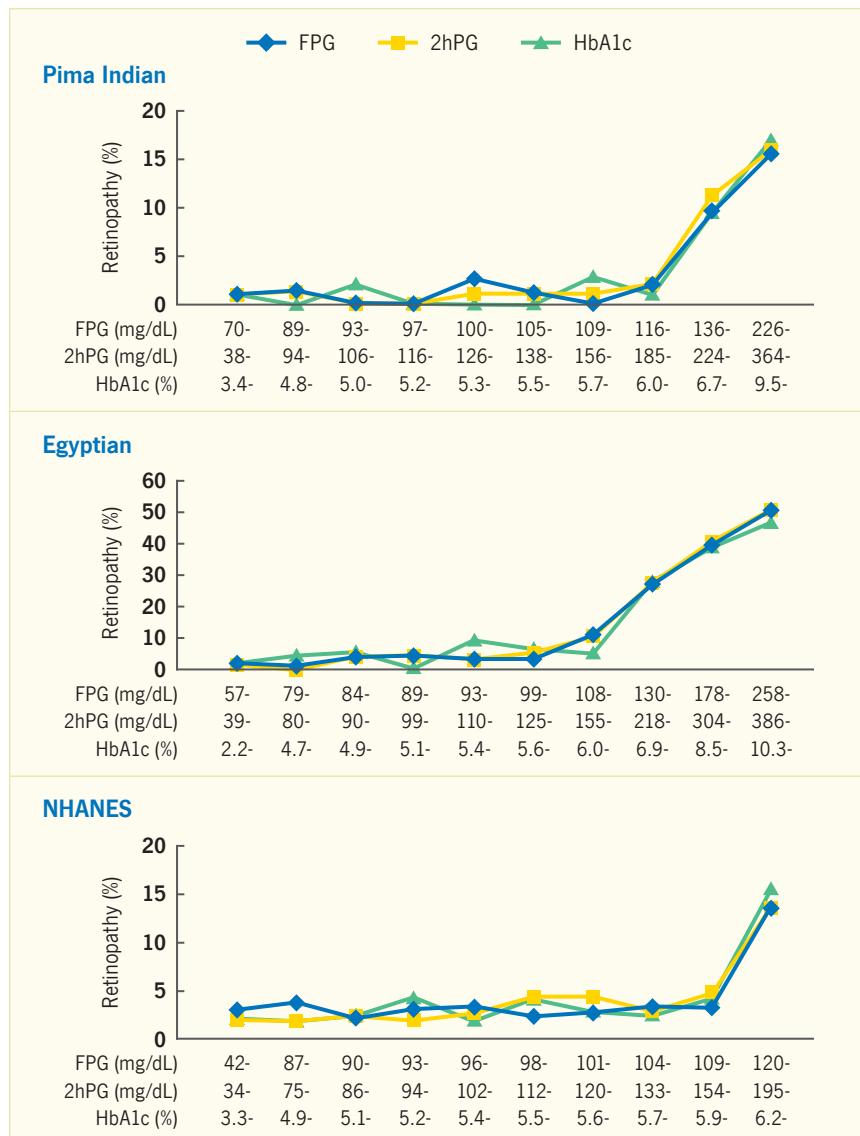
cause glycosuria and polyuria with resultant polydipsia. These symptoms may not occur in type 2 diabetes owing to the slow, progressive rise in glycemia over time; when symptoms are present, they generally are relieved readily by nutritional and pharmacologic therapy. However, the degree of residual 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 ≥ 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.

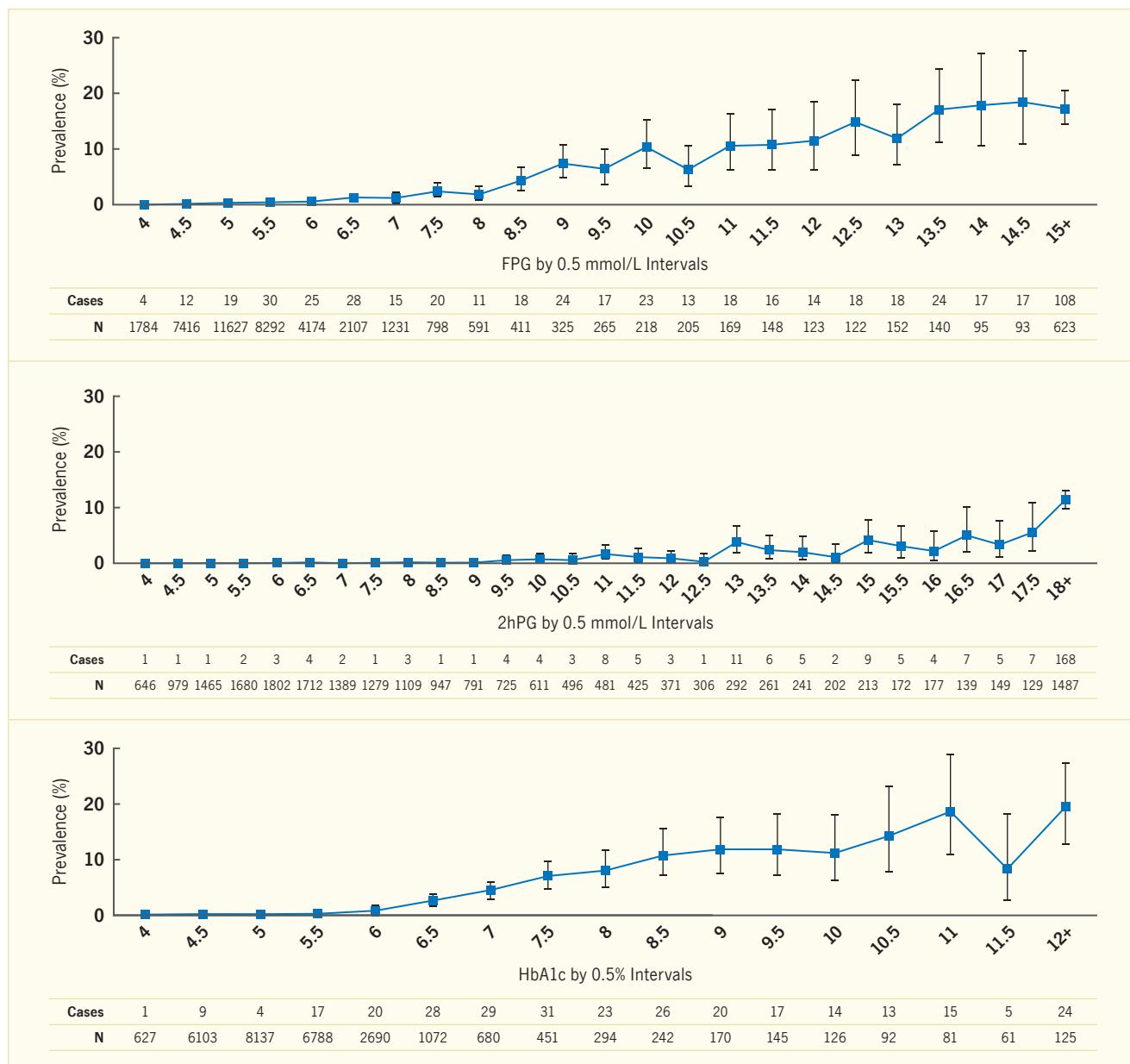
By 2009, an IEC constituted by the ADA and European Association for the Study of Diabetes judged that the above two impediments had been removed (35). The National Glycohemoglobin Standardization Program (NGSP) (36) had evaluated and standardized the most common A1c assays against the assay employed 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.

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

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

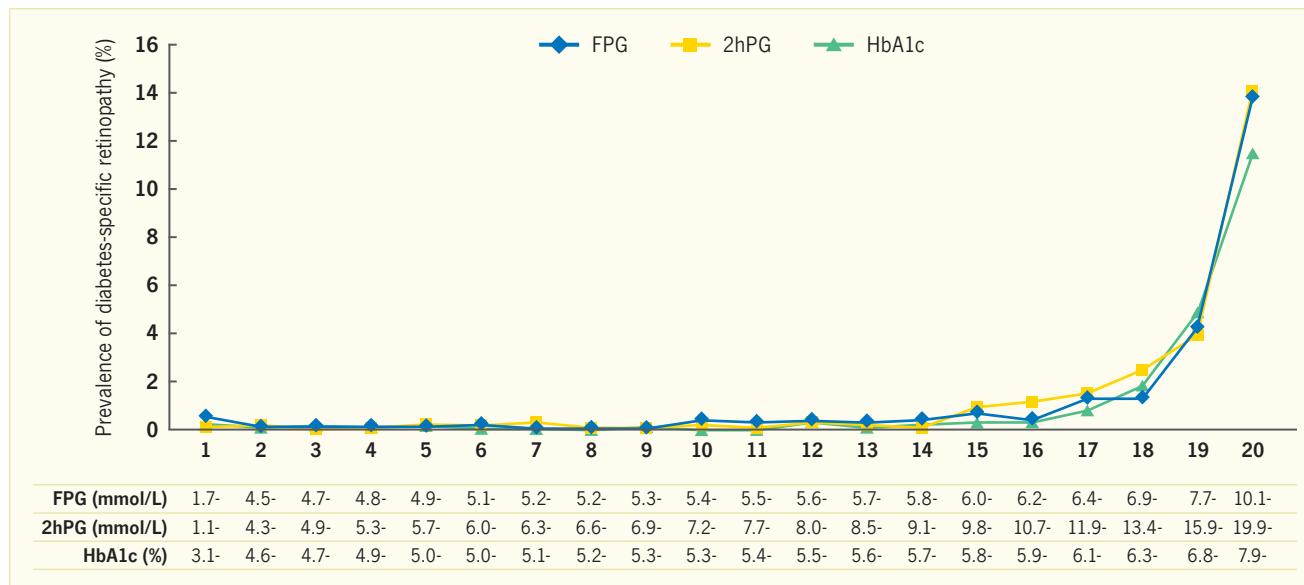
In addition to the standardization and improvements in the A1c assay, the data base comparing the level of A1c to the prevalence of retinopathy had greatly expanded. The DETECT-2 study created a cohort of 44,623 persons age 20–79 years from both sexes representing four studies from the United States, 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 quintiles 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.

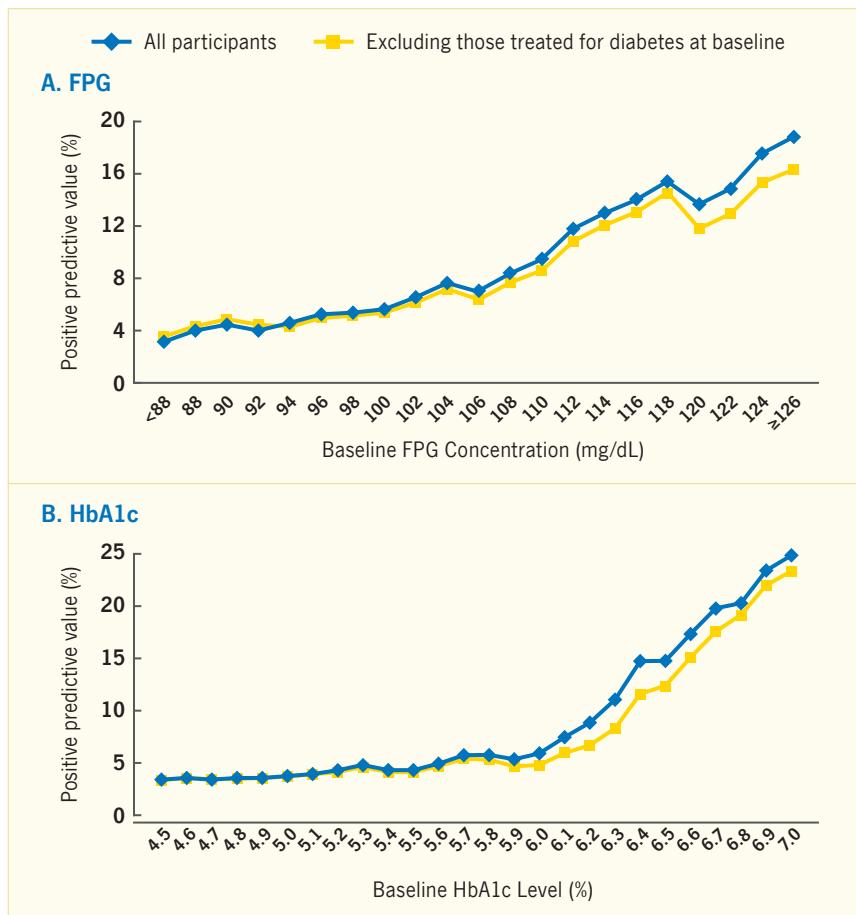
SOURCE: Reference 41, copyright © 2011 American Diabetes Association, reprinted with permission from The American Diabetes Association

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.

SOURCE: Reference 46, copyright © 2011 American Medical Association, reproduced with permission. All rights reserved.

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

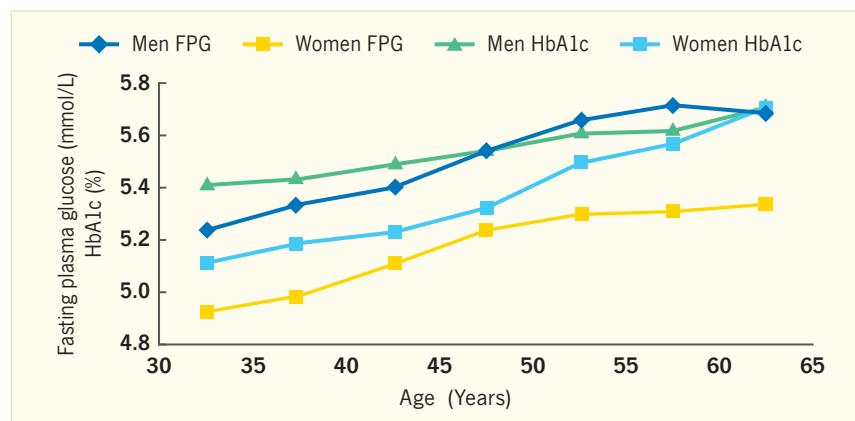
Certain caveats regarding A1c must be highlighted, as it can be influenced by factors other than glycemia (Table 1.5) (37,38). In nondiabetic persons, A1c has been shown to increase with age in multiple cross-sectional studies including: the Framingham Offspring Study, in which an increase of 0.10%–0.14% 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

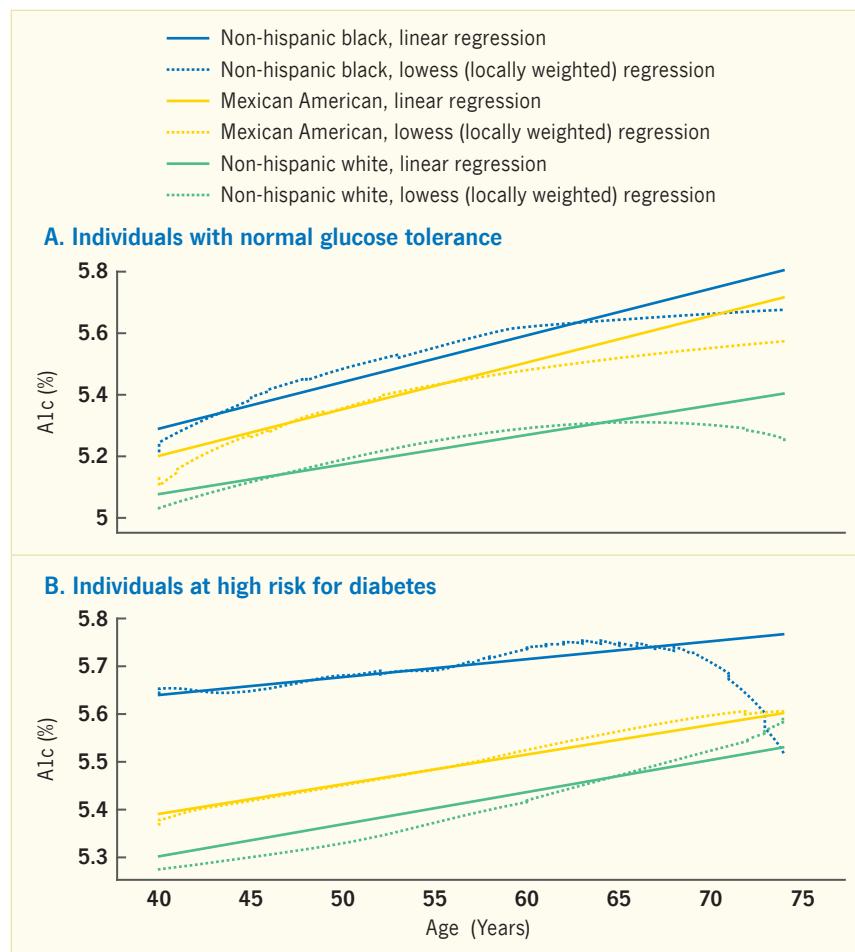
FIGURE 1.6. HbA1c and Fasting Plasma Glucose, by Age and Sex, DESIR Study, 1994–2005



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

races 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 glycators” have higher A1c levels than would be predicted based on the glucose levels, and those defined as “low glycators” have lower A1c levels than would have been predicted from their glucose levels. The boundaries of these abnormal glycator 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 glycated molecule reflecting glycemic levels in the previous 2–3 weeks, can be substituted for MPG in such ratios (87). Persistence of low and high glycator 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 ≥ 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 ≥ 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/m²) > 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 auto-fluorescence 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.

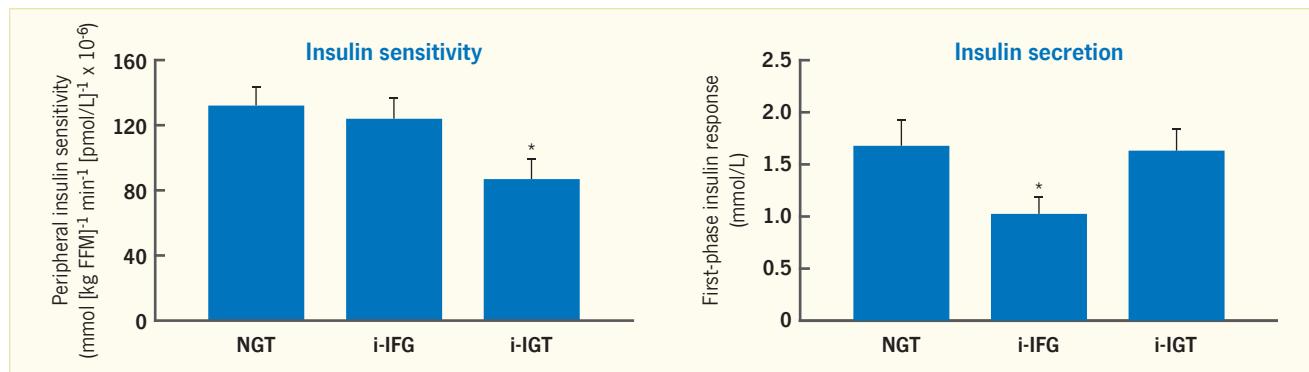
Genetic Testing

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

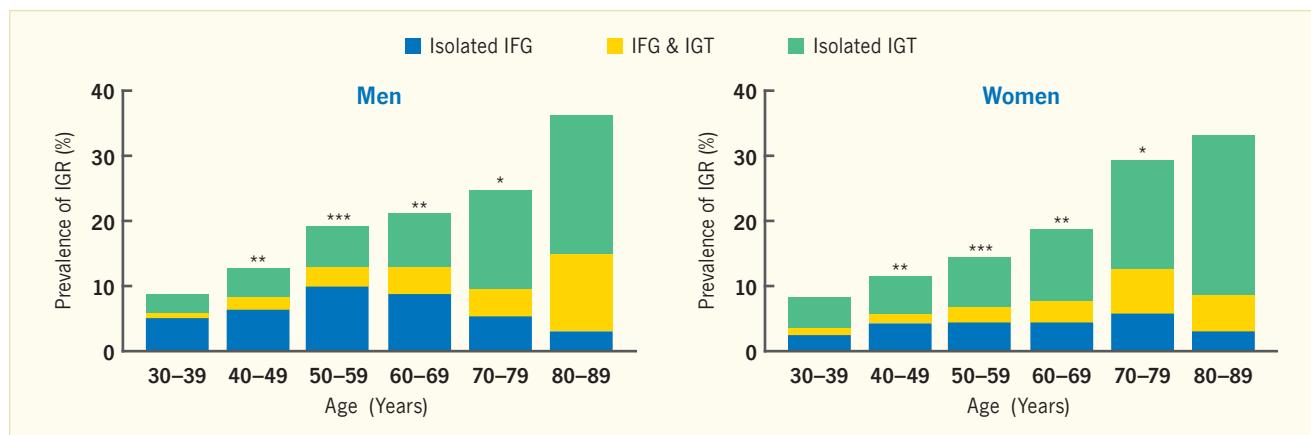
CHARACTERISTICS	PERCENT			
	IGT or IFG*	IGT*	IFG*	A1c†
Age (years)				
≥ 20	29.5	13.8	25.7	3.4
≥ 65	40.4	26.9	36.6	8.1
Sex				
Men	36.0	14.6	32.1	3.6
Women	23.4	13.1	19.8	3.2
Race/ethnicity				
Non-Hispanic white	29.3	14.5	25.8	2.7
Non-Hispanic black	25.1	10.0	20.5	7.2
Mexican American	31.7	13.0	26.8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

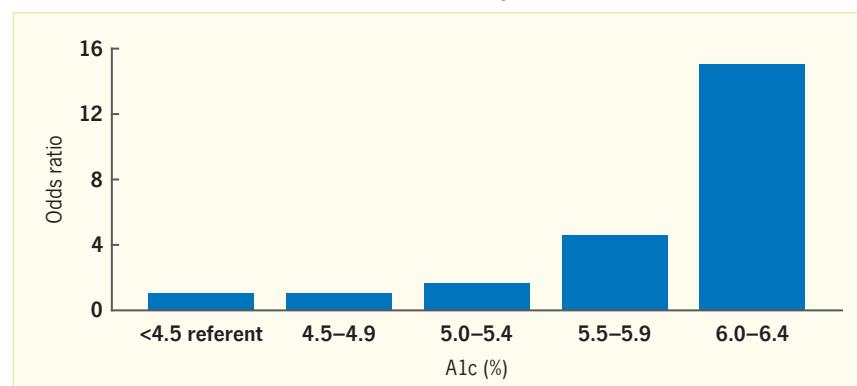
TABLE 1.11. A1c as a Risk Factor for Incident Type 2 Diabetes

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 6.0–6.4	4.9 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 6.0–6.4	3.8 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



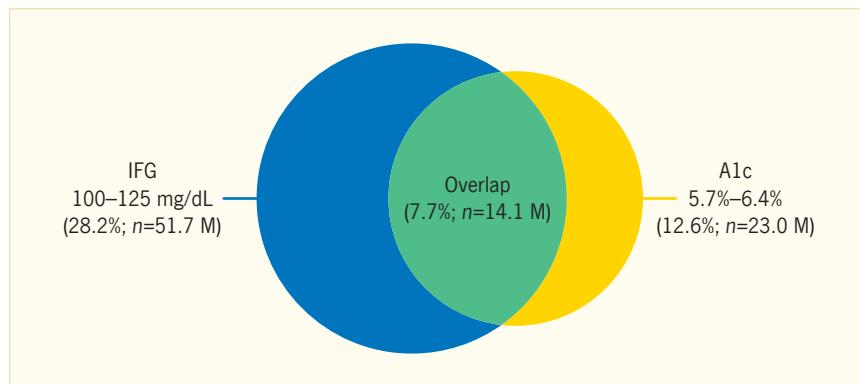
Data from a Veterans Administration study are presented as odds ratios of diabetes incidence versus A1c relative to a referent A1c of <4.5%. Conversions for A1c values are provided in *Diabetes in America Appendix 1 Conversions*. A1c, glycated hemoglobin.

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.

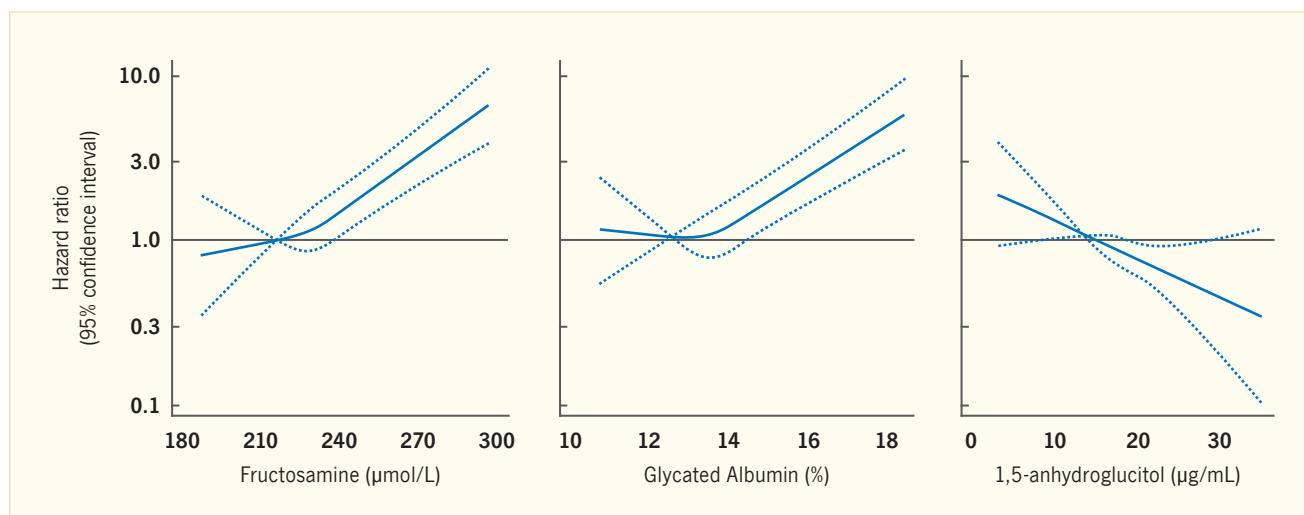
Other Glycemic Risk Factors for Diabetes

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 lifestyle 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 $\geq 25 \text{ kg/m}^2$	Polycystic ovaries
High-risk ethnicity	Hypertension
First-degree relatives with diabetes	History of cardiovascular disease
Age ≥ 45 years	HDL cholesterol $\leq 35 \text{ mg/dL}$ and/or triglycerides $\geq 250 \text{ mg/dL}$
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 DPPOS, 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.

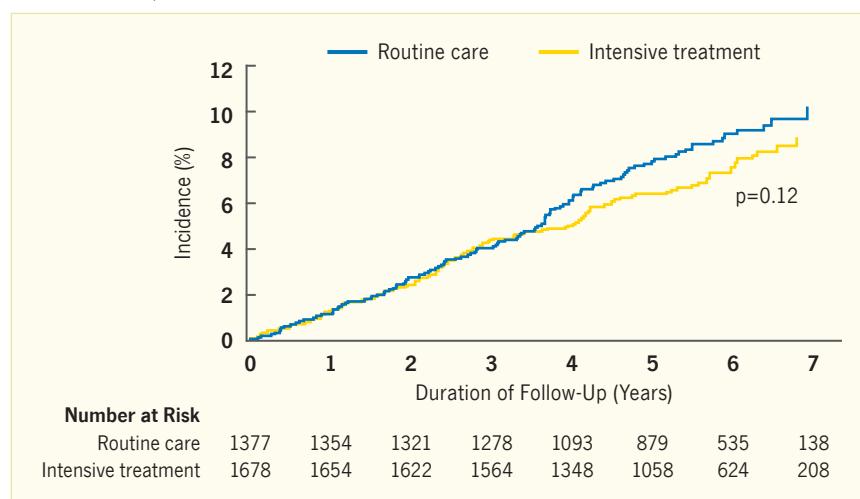
Other Health Care Venues

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.

SOURCE: Reference 258, reprinted from *The Lancet* copyright © 2011, with permission from Elsevier

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 Diamicron 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 life-style 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 ≥ 126 mg/dL and/or 2-hour SG ≥ 200 mg/dL. CBG ≥ 140 mg/dL was 56%–65% sensitive and 95%–96% specific for diabetes compared to the OGTT criteria. CBG ≥ 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 ≥ 126 mg/dL. A random plasma glucose ≥ 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 ≥ 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).

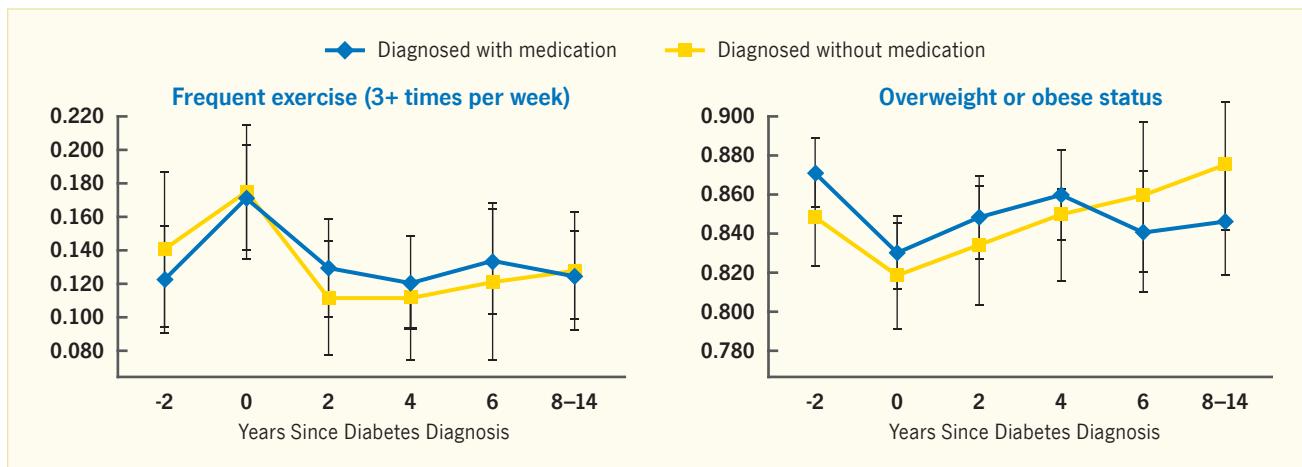
The use of A1c as a screening test has been supported in screening studies of Native American (267), Hong Kong Chinese (268), and Abu Dhabi (269) populations with and without pairing with FPG. Population-specific optimal cutpoints are described, but generalization to worldwide screening definitions is uncertain. In a study of the NHANES 1988–1994 cohort, compared to FPG ≥ 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 Screeners

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.

SOURCE: Reference 283, copyright © 2012 Elsevier, reprinted with permission

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

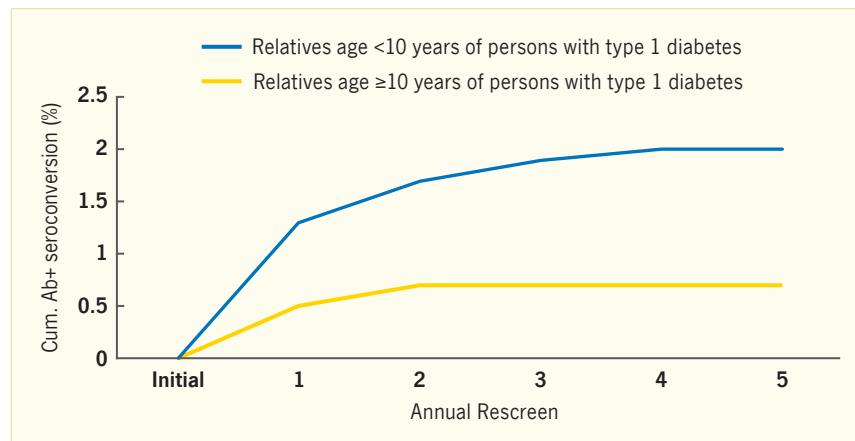
Screening for type 1 diabetes in the general population is not recommended by the ADA on the grounds that relatively few cases would be detected (263). Screening of offspring or siblings (or other relatives) of patients with type 1 diabetes with multiple islet cell autoantibodies, if requested by parents, 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.

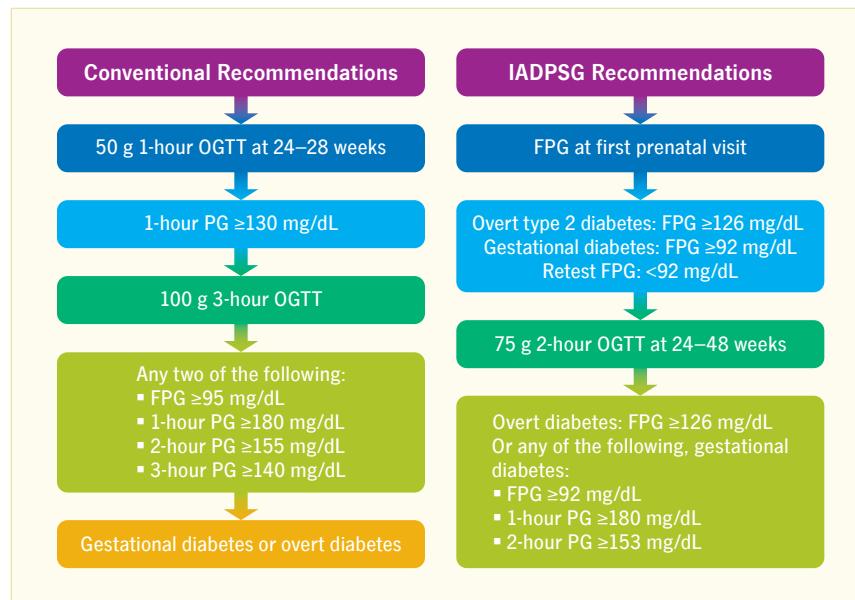
The addition of ZnT8 autoantibodies to the now-traditional other biochemical autoantibodies (i.e., GAD, insulin, IA-2) and ICA improves screening for preclinical type 1 diabetes (289). Moreover, a risk score for the development of diabetes in autoantibody-positive relatives of type 1 diabetic individuals 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
DEISR	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.

REFERENCES

1. Centers for Disease Control and Prevention: *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, 2014
2. Geiss LS, Wang J, Cheng YJ, Thompson TJ, Barker L, Li Y, Albright AL, Gregg EW: Prevalence and incidence trends for diagnosed diabetes among adults aged 20 to 79 years, United States, 1980–2012. *JAMA* 312:1218–1226, 2014
3. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
4. Dunstan DW, Zimmet PZ, Welborn TA, De Courten MP, Cameron AJ, Sicree RA, Dwyer T, Colagiuri S, Jolley D, Knuiman M, Atkins R, Shaw JE: The rising prevalence of diabetes and impaired glucose tolerance: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 25:829–834, 2002
5. American Diabetes Association: Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 36:1033–1046, 2013
6. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 36(Suppl 1):S67–S74, 2013
7. Imagawa A, Hanafusa T, Miyagawa J, Matsuzawa Y; Osaka IDDM Study Group: A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence of diabetes-related autoantibodies. *N Engl J Med* 342:301–307, 2000
8. Greenbaum CJ, Cuthbertson D, Krischer JP; Disease Prevention Trial of Type 1 Diabetes Study Group: Type 1 diabetes manifested solely by 2-h oral glucose tolerance test criteria. *Diabetes* 50:470–476, 2001
9. The Diabetes Prevention Trial-Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002
10. Greenbaum CJ, Beam CA, Boulware D, Gitelman SE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steinrauf H, Skyler JS, Sosenko JM; Type 1 Diabetes TrialNet Study Group: Fall in c-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. *Diabetes* 61:2066–2073, 2012
11. Oram RA, Jones AG, Besser RE, Knight BA, Shields BM, Brown RJ, Hattersley AT, McDonald TJ: The majority of patients with long-duration type 1 diabetes are insulin microsecretors and have functioning beta cells. *Diabetologia* 57:187–191, 2014
12. Wang L, Lovejoy NF, Faustman DL: Persistence of prolonged c-peptide production in type 1 diabetes as measured with an ultrasensitive c-peptide assay. *Diabetes Care* 35:465–470, 2012
13. Davis AK, DuBose SN, Haller MJ, Miller KM, DiMeglio LA, Bethin KE, Goland RS, Greenberg EM, Liljenquist DR, Ahmann AJ, Marcovina SM, Peters AL, Beck RW, Greenbaum CJ; T1D Exchange Clinic Network: Prevalence of detectable c-peptide according to age at diagnosis and duration of type 1 diabetes. *Diabetes Care* 38:476–481, 2015
14. Keenan HA, Sun JK, Levine J, Doria A, Aiello LP, Eisenbarth G, Bonner-Weir S, King GL: Residual insulin production and pancreatic beta-cell turnover after 50 years of diabetes: Joslin Medalist Study. *Diabetes* 59:2846–2853, 2010
15. Weyer C, Bogardus C, Mott DM, Pratley RE: The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 104:787–794, 1999
16. Bellamy L, Casas JP, Hingorani AD, Williams D: Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. *Lancet* 373:1773–1779, 2009
17. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R; UK Prospective Diabetes Study Group: UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. *Lancet* 350:1288–1293, 1997
18. Purnell JQ, Dev RK, Steffes MW, Cleary PA, Palmer JP, Hirsch IB, Hokanson JE, Brunzell JD: Relationship of family history of type 2 diabetes, hypoglycemia, and autoantibodies to weight gain and lipids with intensive and conventional therapy in the Diabetes Control and Complications Trial. *Diabetes* 52:2623–2629, 2003
19. Sosenko JM, Skyler JS, Mahon J, Krischer JP, Beam CA, Boulware DC, Greenbaum CJ, Rafkin LE, Cowie C, Cuthbertson D, Palmer JP; Type 1 Diabetes TrialNet and Diabetes Prevention Trial-Type 1 Study Groups: Validation of the diabetes prevention trial-type 1 risk score in the TrialNet natural history study. *Diabetes Care* 34:1785–1787, 2011
20. Skyler JS, Krischer JP, Wolfsdorf J, Cowie C, Palmer JP, Greenbaum C, Cuthbertson D, Rafkin-Mervis LE, Chase HP, Leschek E: Effects of oral insulin in relatives of patients with type 1 diabetes mellitus: The Diabetes Prevention Trial-Type 1. *Diabetes Care* 28:1068–1076, 2005
21. Gale EA, Bingley PJ, Emmett CL, Collier T; European Nicotinamide Diabetes Intervention Trial (ENDIT) Group: European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 363:925–931, 2004
22. Badaru A, Pihoker C: Type 2 diabetes in childhood: clinical characteristics and role of beta-cell autoimmunity. *Curr Diab Rep* 12:75–81, 2012
23. Borg H, Gottsater A, Fernlund P, Sundkvist G: A 12-year prospective study of the relationship between islet antibodies and beta-cell function at and after the diagnosis in patients with adult-onset diabetes. *Diabetes* 51:1754–1762, 2002
24. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP: Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med* 159:1450–1456, 1999
25. Cheng YJ, Imperatore G, Geiss LS, Wang J, Saydah SH, Cowie CC, Gregg EW: Secular changes in the age-specific prevalence of diabetes among U.S. adults: 1988–2010. *Diabetes Care* 36:2690–2696, 2013
26. Flegal KM, Carroll MD, Kit BK, Ogden CL: Prevalence of obesity and trends in the distribution of body mass index among U.S. adults, 1999–2010. *JAMA* 307:491–497, 2012
27. Menke A, Rust KF, Fradkin J, Cheng YJ, Cowie CC: Associations between trends in race/ethnicity, aging, and body mass index with diabetes prevalence in the United States: a series of cross-sectional studies. *Ann Intern Med* 161:328–335, 2014
28. Bonnefond A, Froguel P: Rare and common genetic events in type 2 diabetes: what should biologists know? *Cell Metab* 21:357–368, 2015
29. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

30. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 44:968–983, 1995
31. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
32. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–412, 2000
33. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 20:1183–1197, 1997
34. Peters AL, Davidson MB, Schriger DL, Hasselblad V; Meta-analysis Research Group on the Diagnosis of Diabetes Using Glycated Hemoglobin Levels: A clinical approach for the diagnosis of diabetes mellitus: an analysis using glycosylated hemoglobin levels. *JAMA* 276:1246–1252, 1996
35. International Expert Committee: International expert committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care* 32:1327–1334, 2009
36. Little RR, Rohlfing CL, Wiedmeyer HM, Myers GL, Sacks DB, Goldstein DE; NGSP Steering Committee: The national glycohemoglobin standardization program: a five-year progress report. *Clin Chem* 47:1985–1992, 2001
37. World Health Organization: Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva, WHO Press, 2011
38. Gallagher EJ, Le Roith D, Bloomgarden Z: Review of hemoglobin A1c in the management of diabetes. *J Diabetes* 1:9–17, 2009
39. Steffes M, Cleary P, Goldstein D, Little R, Wiedmeyer HM, Rohlfing C, England J, Bucksa J, Nowicki M: Hemoglobin A1c measurements over nearly two decades: sustaining comparable values throughout the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study. *Clin Chem* 51:753–758, 2005
40. American Diabetes Association: (2) Classification and diagnosis of diabetes. *Diabetes Care* 38(Suppl):S8–S16, 2015
41. Colaguri S, Lee CM, Wong TY, Balkau B, Shaw JE, Borch-Johnsen K; DETECT-2 Collaboration Writing Group: Glycemic thresholds for diabetes-specific retinopathy: implications for diagnostic criteria for diabetes. *Diabetes Care* 34:145–150, 2011
42. Sabanayagam C, Liew G, Tai ES, Shankar A, Lim SC, Subramaniam T, Wong TY: Relationship between glycated haemoglobin and microvascular complications: is there a natural cut-off point for the diagnosis of diabetes? *Diabetologia* 52:1279–1289, 2009
43. Cheng YJ, Gregg EW, Geiss LS, Imperatore G, Williams DE, Zhang X, Albright AL, Cowie CC, Klein R, Saaddine JB: Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population: implications for diabetes diagnostic thresholds. *Diabetes Care* 32:2027–2032, 2009
44. Sacks DB: The diagnosis of diabetes is changing: how implementation of hemoglobin A1c will impact clinical laboratories. *Clin Chem* 55:1612–1614, 2009
45. Selvin E, Crainiceanu CM, Brancati FL, Coresh J: Short-term variability in measures of glycemia and implications for the classification of diabetes. *Arch Intern Med* 167:1545–1551, 2007
46. Massin P, Lange C, Tichet J, Vol S, Erginay A, Cailleau M, Eschwege E, Balkau B; DESIR (Data From an Epidemiological Study on the Insulin Resistance Syndrome) Study Group: Hemoglobin A1c and fasting plasma glucose levels as predictors of retinopathy at 10 years: the French DESIR study. *Arch Ophthalmol* 129:188–195, 2011
47. Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Kirkman MS, Lernmark A, Metzger BE, Nathan DM: Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Clin Chem* 57:e1–e47, 2011
48. Greaves RF, Northfield JA, Cameron FJ: Haemoglobin A1c: evaluation of three point of care analysers for use in a paediatric diabetes clinic. *Ann Clin Biochem* 42:124–129, 2005
49. Bode BW, Irvin BR, Pierce JA, Allen M, Clark AL: Advances in hemoglobin A1c point of care technology. *J Diabetes Sci Technol* 1:405–411, 2007
50. Sanchez-Mora C, S Rodriguez-Oliva M, Fernandez-Riejos P, Mateo J, Polo-Padillo J, Goberna R, Sanchez-Margalef V: Evaluation of two HbA1c point-of-care analyzers. *Clin Chem Lab Med* 49:653–657, 2011
51. Wood JR, Kaminski BM, Kollman C, Beck RW, Hall CA, Yun JP, Cengiz E, Haller MJ, Hassan K, Klingensmith GJ, Tamborlane WV: Accuracy and precision of the Axis-Shield Afinion hemoglobin A1c measurement device. *J Diabetes Sci Technol* 6:380–386, 2012
52. Affret A, Griz LH, Cesse EA, Specht YD, Carvalho EM, Fontbonne A: Assessment of a glycated hemoglobin point-of-care analyzer (A1CNow+) in comparison with an immunoturbidimetric method: a diagnostic accuracy study. *Sao Paulo Med J* 111:460–464, 2015
53. Manley SE, Hikin LJ, Round RA, Manning PW, Luzio SD, Dunseath GJ, Nightingale PG, Stratton IM, Cramb R, Sikaris KA, Gough SC, Webber J: Comparison of IFCC-calibrated HbA1c from laboratory and point of care testing systems. *Diabetes Res Clin Pract* 105:364–372, 2014
54. Wan Mohd Zin RM, Ahmad Kamil ZI, Tuan Soh TR, Emborg M, Wan Mohamud WN: Haemoglobin A1c: comparing performance of two point of care devices with laboratory analyser. *BMC Res Notes* 6:540, 2013
55. Haliassos A, Drakopoulos I, Katritsis D, Chiotinis N, Korovesis S, Makris K: Measurement of glycated hemoglobin (HbA1c) with an automated POCT instrument in comparison with HPLC and automated immunochemistry method: evaluation of the influence of hemoglobin variants. *Clin Chem Lab Med* 44:223–227, 2006
56. Lenters-Westra E, Slingerland RJ: Six of eight hemoglobin A1c point-of-care instruments do not meet the general accepted analytical performance criteria. *Clin Chem* 56:44–52, 2010
57. Little RR: Analysis of the accuracy and precision of the Axis-Shield Afinion hemoglobin A1c measurement device. *J Diabetes Sci Technol* 6:387–388, 2012
58. Dupuy AM, Badiou S, Elong-Bertard C, Bargnoux AS, Cristol JP: Analytical performance of the Axis-Shield Afinion for hemoglobin A1c measurement: impact of lot number. *Clin Lab* 60:369–376, 2014
59. Solvik UO, Roraas T, Christensen NG, Sandberg S: Diagnosing diabetes mellitus: performance of hemoglobin A1c point-of-care instruments in general practice offices. *Clin Chem* 59:1790–1801, 2013
60. Pani LN, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, Sullivan L, D'Agostino RB, Nathan DM: Effect of aging on A1C levels in individuals without diabetes: evidence from the Framingham Offspring Study and the National Health and Nutrition Examination Survey 2001–2004. *Diabetes Care* 31:1991–1996, 2008

61. Gusto G, Vol S, Born C, Balkau B, Lamy J, Bourderiou C, Lantieri O, Tichet J: [Age and sex variations of HbA1C] in a French population without known diabetes aged 6 to 79 years]. [Article in French] *Ann Biol Clin (Paris)* 69:545–553, 2011
62. Balkau B, Soulimane S, Lange C, Gautier A, Tichet J, Vol S; DESIR Study Group: Are the same clinical risk factors relevant for incident diabetes defined by treatment, fasting plasma glucose, and HbA1c? *Diabetes Care* 34:957–959, 2011
63. Snieder H, Sawtell PA, Ross L, Walker J, Spector TD, Leslie RD: HbA1c levels are genetically determined even in type 1 diabetes: evidence from healthy and diabetic twins. *Diabetes* 50:2858–2863, 2001
64. Paterson AD, Waggott D, Boright AP, Hosseini SM, Shen E, Sylvestre MP, Wong I, Bharaj B, Cleary PA, Lachin JM; MAGIC (Meta-Analyses of Glucose and Insulin-related traits Consortium), Below JE, Nicolae D, Cox NJ, Carty AJ, Sun L, Bull SB; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: A genome-wide association study identifies a novel major locus for glycemic control in type 1 diabetes, as measured by both A1C and glucose. *Diabetes* 59:539–549, 2010
65. Davidson MB, Schriger DL: Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. *Diabetes Res Clin Pract* 87:415–421, 2010
66. Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES, Lachin JM, Montez MG, Brenneman T, Barrett-Connor E; Diabetes Prevention Program Research Group: Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care* 30:2453–2457, 2007
67. Ziemer DC, Kolm P, Weintraub WS, Vaccarino V, Rhee MK, Twombly JG, Narayan KM, Koch DD, Phillips LS: Glucose-independent, black-white differences in hemoglobin A1c levels: a cross-sectional analysis of 2 studies. *Ann Intern Med* 152:770–777, 2010
68. Selvin E, Steffes MW, Ballantyne CM, Hoogeveen RC, Coresh J, Brancati FL: Racial differences in glycemic markers: a cross-sectional analysis of community-based data. *Ann Intern Med* 154:303–309, 2011
69. Tsugawa Y, Mukamal KJ, Davis RB, Taylor WC, Wee CC: Should the hemoglobin A1c diagnostic cutoff differ between blacks and whites? A cross-sectional study. *Ann Intern Med* 157:153–159, 2012
70. Bower JK, Brancati FL, Selvin E: No ethnic differences in the association of glycated hemoglobin with retinopathy: the National Health and Nutrition Examination Survey 2005–2008. *Diabetes Care* 36:569–573, 2013
71. Tseng CL, Brimacombe M, Xie M, Rajan M, Wang H, Kolassa J, Crystal S, Chen TC, Pogach L, Safford M: Seasonal patterns in monthly hemoglobin A1c values. *Am J Epidemiol* 161:565–574, 2005
72. Sohmiya M, Kanazawa I, Kato Y: Seasonal changes in body composition and blood HbA1c levels without weight change in male patients with type 2 diabetes treated with insulin. *Diabetes Care* 27:1238–1239, 2004
73. Lukens JN: The abnormal hemoglobins: general principles. In *Wintrobe's Clinical Hematology*. 11th ed. Greer JP, Foerster J, Lukens JN, Rodgers GM, Paraskevas F, Glader B, Eds. Philadelphia, Lippincott Williams & Wilkins, 2004, p. 1247–1262
74. Sacks DB: A1C versus glucose testing: a comparison. *Diabetes Care* 34:518–523, 2011
75. Norman BJ, Miller SD: Human genome project and sickle cell disease. *Soc Work Public Health* 26:405–416, 2011
76. Virtue MA, Furne JK, Nuttall FQ, Levitt MD: Relationship between GHb concentration and erythrocyte survival determined from breath carbon monoxide concentration. *Diabetes Care* 27:931–935, 2004
77. Cohen RM, Franco RS, Khera PK, Smith EP, Lindsell CJ, Ciraolo PJ, Palascak MB, Joiner CH: Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. *Blood* 112:4284–4291, 2008
78. El-Agouza I, Abu Shahla A, Sirdah M: The effect of iron deficiency anaemia on the levels of haemoglobin subtypes: possible consequences for clinical diagnosis. *Clin Lab Haematol* 24:285–289, 2002
79. Coban E, Ozdogan M, Timuragaoglu A: Effect of iron deficiency anemia on the levels of hemoglobin A1c in nondiabetic patients. *Acta Haematol* 112:126–128, 2004
80. Kim C, Bullard KM, Herman WH, Beckles GL: Association between iron deficiency and A1C levels among adults without diabetes in the National Health and Nutrition Examination Survey, 1999–2006. *Diabetes Care* 33:780–785, 2010
81. Szymczak J, Lavalard E, Martin M, Leroy N, Gillery P: Carbamylated hemoglobin remains a critical issue in HbA1c measurements. *Clin Chem Lab Med* 47:612–613, 2009
82. Meijis MF, Dijkhorst-Oei LT, van Loo R, Bosma RJ, Weykamp CW, Wielders JP: Does carbamylated hemoglobin still affect the analysis of HbA1c in uremic and hyperglycemic patients? *Clin Chem Lab Med* 46:1791–1792, 2008
83. Cohen RM, LeCaire TJ, Lindsell CJ, Smith EP, D'Alessio DJ: Relationship of prospective GHb to glycated serum proteins in incident diabetic retinopathy: implications of the glycation gap for mechanism of risk prediction. *Diabetes Care* 31:151–153, 2008
84. Hudson PR, Child DF, Jones H, Williams CP: Differences in rates of glycation (glycation index) may significantly affect individual HbA1c results in type 1 diabetes. *Ann Clin Biochem* 36:451–459, 1999
85. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Wilson DM, Xing D, Beck RW, Block J, Bode B, Fox LA, Hirsch I, Kollman C, Laffel L, Ruedy KJ, Steffes M, Tamborlane WV: Hemoglobin A1c and mean glucose in patients with type 1 diabetes: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring randomized trial. *Diabetes Care* 34:540–544, 2011
86. Wilson DM, Xing D, Cheng J, Beck RW, Hirsch I, Kollman C, Laffel L, Lawrence JM, Maura N, Ruedy KJ, Tsaliakian E, Wolpert H; Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: Persistence of individual variations in glycated hemoglobin: analysis of data from the Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Randomized Trial. *Diabetes Care* 34:1315–1317, 2011
87. Cohen RM, Holmes YR, Chenier TC, Joiner CH: Discordance between HbA1c and fructosamine: evidence for a glycosylation gap and its relation to diabetic nephropathy. *Diabetes Care* 26:163–167, 2003
88. Kilpatrick ES, Rigby AS, Atkin SL: Variability in the relationship between mean plasma glucose and HbA1c: implications for the assessment of glycemic control. *Clin Chem* 53:897–901, 2007
89. Hempe JM, Gomez R, McCarter RJ, Jr., Chalew SA: High and low hemoglobin glycation phenotypes in type 1 diabetes: a challenge for interpretation of glycemic control. *J Diabetes Complications* 16:313–320, 2002

90. McCarter RJ, Hempe JM, Gomez R, Chalew SA: Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes. *Diabetes Care* 27:1259–1264, 2004
91. Lachin JM, Genuth S, Nathan DM, Rutledge BN: The hemoglobin glycation index is not an independent predictor of the risk of microvascular complications in the Diabetes Control and Complications Trial. *Diabetes* 56:1913–1921, 2007
92. Genuth S, Lachin JM, Nathan DM: Biological variation in HbA1c predicts risk of retinopathy and nephropathy in type 1 diabetes: response to McCarter et al. *Diabetes Care* 28:233, 2005
93. Cowie CC, Rust KF, Ford ES, Eberhardt MS, Byrd-Holt DD, Li C, Williams DE, Gregg EW, Bainbridge KE, Saydah SH, Geiss LS: Full accounting of diabetes and pre-diabetes in the U.S. population in 1988–1994 and 2005–2006. *Diabetes Care* 32:287–294, 2009
94. Cowie CC, Rust KF, Byrd-Holt DD, Gregg EW, Ford ES, Geiss LS, Bainbridge KE, Fradkin JE: Prevalence of diabetes and high risk for diabetes using A1C criteria in the U.S. population in 1988–2006. *Diabetes Care* 33:562–568, 2010
95. Olson DE, Rhee MK, Herrick K, Ziemer DC, Twombly JG, Phillips LS: Screening for diabetes and pre-diabetes with proposed A1C-based diagnostic criteria. *Diabetes Care* 33:2184–2189, 2010
96. Cohen RM, Haggerty S, Herman WH: HbA1c for the diagnosis of diabetes and prediabetes: is it time for a mid-course correction? *J Clin Endocrinol Metab* 95:5203–5206, 2010
97. Malkani S, DeSilva T: Controversies on how diabetes is diagnosed. *Curr Opin Endocrinol Diabetes Obes* 19:97–103, 2012
98. Lapolla A, Mosca A, Fedele D: The general use of glycated haemoglobin for the diagnosis of diabetes and other categories of glucose intolerance: still a long way to go. *Nutr Metab Cardiovasc Dis* 21:467–475, 2011
99. Fonseca V, Inzucchi SE, Ferrannini E: Redefining the diagnosis of diabetes using glycated hemoglobin. *Diabetes Care* 32:1344–1345, 2009
100. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes Care* 28:1039–1057, 1979
101. Finch CF, Zimmet PZ, Alberti KG: Determining diabetes prevalence: a rational basis for the use of fasting plasma glucose concentrations? *Diabet Med* 7:603–610, 1990
102. Genuth S, Alberti KG, Bennett P, Buse J, DeFranzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P; Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
103. Unwin N, Shaw J, Zimmet P, Alberti KG: Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 19:708–723, 2002
104. Tietz Textbook of Clinical Chemistry. 3rd ed. Burtis CA, Ashwood ER, Eds. Philadelphia, PA, W.B. Saunders, 1999
105. Rosenbloom AL, Joe JR, Young RS, Winter WE: Emerging epidemic of type 2 diabetes in youth. *Diabetes Care* 22:345–354, 1999
106. Wiegand S, Maikowski U, Blankenstein O, Biebermann H, Tarnow P, Gruters A: Type 2 diabetes and impaired glucose tolerance in European children and adolescents with obesity—a problem that is no longer restricted to minority groups. *Eur J Endocrinol* 151:199–206, 2004
107. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF; SEARCH for Diabetes in Youth Study: Prevalence of type 1 and type 2 diabetes among children and adolescents from 2001 to 2009. *JAMA* 311:1778–1786, 2014
108. Demmer RT, Zuk AM, Rosenbaum M, Desvarieux M: Prevalence of diagnosed and undiagnosed type 2 diabetes mellitus among US adolescents: results from the continuous NHANES, 1999–2010. *Am J Epidemiol* 178:1106–1113, 2013
109. Copeland KC, Zeitzer P, Geffner M, Guandalini C, Higgins J, Hirst K, Kaufman FR, Linder B, Marcovina S, McGuigan P, Pyle L, Tamborlane W, Willi S; TODAY Study Group: Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab* 96:159–167, 2011
110. Nowicka P, Santoro N, Liu H, Lartaud D, Shaw MM, Goldberg R, Guandalini C, Savoye M, Rose P, Caprio S: Utility of hemoglobin A1c(1c) for diagnosing prediabetes and diabetes in obese children and adolescents. *Diabetes Care* 34:1306–1311, 2011
111. Krakoff J, Hanson RL, Kobes S, Knowler WC: Comparison of the effect of plasma glucose concentrations on microvascular disease between Pima Indian youths and adults. *Diabetes Care* 24:1023–1028, 2001
112. Kapadia CR: Are the ADA hemoglobin A1c criteria relevant for the diagnosis of type 2 diabetes in youth? *Curr Diab Rep* 13:51–55, 2013
113. Kester LM, Hey H, Hannon TS: Using hemoglobin A1c for prediabetes and diabetes diagnosis in adolescents: can adult recommendations be upheld for pediatric use? *J Adolesc Health* 50:321–323, 2012
114. Lee JM, Wu EL, Tarini B, Herman WH, Yoon E: Diagnosis of diabetes using hemoglobin A1c: should recommendations in adults be extrapolated to adolescents? *J Pediatr* 158:947–952, 2011
115. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W: Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. *Diabetes Care* 32:1626–1631, 2009
116. O’Shea D, O’Connell J: Cystic fibrosis related diabetes. *Curr Diab Rep* 14:511, 2014
117. Burgess JC, Bridges N, Banya W, Gyi KM, Hodson ME, Bilton D, Simmonds NJ: HbA1c as a screening tool for cystic fibrosis related diabetes. *J Cyst Fibros* 15:251–257, 2016
118. Kramer CK, Araneta MR, Barrett-Connor E: A1C and diabetes diagnosis: The Rancho Bernardo Study. *Diabetes Care* 33:101–103, 2010
119. Carson AP, Reynolds K, Fonseca VA, Muntner P: Comparison of A1C and fasting glucose criteria to diagnose diabetes among U.S. adults. *Diabetes Care* 33:95–97, 2010
120. Wang W, Lee ET, Howard BV, Fabsitz RR, Devereux RB, Welty TK: Fasting plasma glucose and hemoglobin A1c in identifying and predicting diabetes: the Strong Heart Study. *Diabetes Care* 34:363–368, 2011
121. Barr RG, Nathan DM, Meigs JB, Singer DE: Tests of glycemia for the diagnosis of type 2 diabetes mellitus. *Ann Intern Med* 137:263–272, 2002
122. Soulimane S, Simon D, Shaw JE, Zimmet PZ, Vol S, Vistisen D, Magliano DJ, Borch-Johnsen K, Balkau B: Comparing incident diabetes as defined by fasting plasma glucose or by HbA1c. The AusDiab, Inter99 and DESIR studies. *Diabet Med* 28:1311–1318, 2011
123. Christensen DL, Witte DR, Kaduka L, Jorgensen ME, Borch-Johnsen K, Mohan V, Shaw JE, Tabak AG, Vistisen D: Moving to an A1C-based diagnosis of diabetes has a different impact on prevalence in different ethnic groups. *Diabetes Care* 33:580–582, 2010

124. DECODE Study Group: Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. *Diabetes Care* 26:61–69, 2003
125. Yang C, Li H, Wang Z, Zhang W, Zhou K, Meng J, Zhao Y, Pan J, Lv X, Liang H, Jiang X: Glycated albumin is a potential diagnostic tool for diabetes mellitus. *Clin Med (Lond.)* 12:568–571, 2012
126. Furusyo N, Koga T, Ai M, Otokozawa S, Kohzuma T, Ikezaki H, Schaefer EJ, Hayashi J: Utility of glycated albumin for the diagnosis of diabetes mellitus in a Japanese population study: results from the Kyushu and Okinawa Population Study (KOPS). *Diabetologia* 54:3028–3036, 2011
127. Meerwaldt R, Links T, Graaff R, Thorpe SR, Baynes JW, Hartog J, Gans R, Smit A: Simple noninvasive measurement of skin autofluorescence. *Ann N Y Acad Sci* 1043:290–298, 2005
128. Orchard TJ, Lyons TJ, Cleary PA, Briffett BH, Maynard J, Cowie C, Gubitosi-Klug RA, Way J, Anderson K, Barnie A, Villavicencio S; DCCT/EDIC Research Group: The association of skin intrinsic fluorescence with type 1 diabetes complications in the DCCT/EDIC study. *Diabetes Care* 36:3146–3153, 2013
129. Conway BN, Aroda VR, Maynard JD, Matter N, Fernandez S, Ratner RE, Orchard TJ: Skin intrinsic fluorescence is associated with coronary artery disease in individuals with long duration of type 1 diabetes. *Diabetes Care* 35:2331–2336, 2012
130. Sugisawa E, Miura J, Iwamoto Y, Uchigata Y: Skin autofluorescence reflects integration of past long-term glycemic control in patients with type 1 diabetes. *Diabetes Care* 36:2339–2345, 2013
131. Monnier VM, Bautista O, Kenny D, Sell DR, Fogarty J, Dahms W, Cleary PA, Lachin J, Genuth S: Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA1c as markers of diabetic complications. DCCT Skin Collagen Ancillary Study Group. Diabetes Control and Complications Trial. *Diabetes* 48:870–880, 1999
132. Maynard JD, Rohrscheib M, Way JF, Nguyen CM, Ediger MN: Noninvasive type 2 diabetes screening: superior sensitivity to fasting plasma glucose and A1C. *Diabetes Care* 30:1120–1124, 2007
133. Smit AJ, Smit JM, Botterblom GJ, Mulder DJ: Skin autofluorescence based decision tree in detection of impaired glucose tolerance and diabetes. *PLoS One* 8:e65592, 2013
134. Tentouris N, Lathouris P, Lontou S, Tzemos K, Maynard J: Screening for HbA1c-defined prediabetes and diabetes in an at-risk Greek population: performance comparison of random capillary glucose, the ADA diabetes risk test and skin fluorescence spectroscopy. *Diabetes Res Clin Pract* 100:39–45, 2013
135. de Ranitz-Greven WL, Bos DC, Pouck WK, Visser GH, Beulens JW, Biesma DH, de Valk HW: Advanced glycation end products, measured as skin autofluorescence, at diagnosis in gestational diabetes mellitus compared with normal pregnancy. *Diabetes Technol Ther* 14:43–49, 2012
136. Diabetes Prevention Program Research Group: The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. *Diabet Med* 24:137–144, 2007
137. Yu T, Mitchell P, Berry G, Li W, Wang JJ: Retinopathy in older persons without diabetes and its relationship to hypertension. *Arch Ophthalmol* 116:83–89, 1998
138. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Polak BC: Risk factors for incident retinopathy in a diabetic and nondiabetic population: the Hoorn study. *Arch Ophthalmol* 121:245–251, 2003
139. Klein R, Myers CE, Lee KE, Klein BE: 15-year cumulative incidence and associated risk factors for retinopathy in nondiabetic persons. *Arch Ophthalmol* 128:1568–1575, 2010
140. Munch IC, Kessel L, Borch-Johnsen K, Glumer C, Lund-Andersen H, Larsen M: Microvascular retinopathy in subjects without diabetes: the Inter99 Eye Study. *Acta Ophthalmol* 90:613–619, 2012
141. Tapp RJ, Tikellis G, Wong TY, Harper CA, Zimmet PZ, Shaw JE; Australian Diabetes Obesity and Lifestyle Study Group: Longitudinal association of glucose metabolism with retinopathy: results from the Australian Diabetes Obesity and Lifestyle (AusDiab) study. *Diabetes Care* 31:1349–1354, 2008
142. van Leiden HA, Dekker JM, Moll AC, Nijpels G, Heine RJ, Bouter LM, Stehouwer CD, Polak BC: Blood pressure, lipids, and obesity are associated with retinopathy: the Hoorn Study. *Diabetes Care* 25:1320–1325, 2002
143. Ellis JD, Zvandasara T, Leese G, McAlpine R, Macewen CJ, Baines PS, Crombie I, Morris AD; DARTS/MEMO Collaboration: Clues to duration of undiagnosed disease from retinopathy and maculopathy at diagnosis in type 2 diabetes: a cross-sectional study. *Br J Ophthalmol* 95:1229–1233, 2011
144. Harris MI, Klein R, Welborn TA, Knuiman MW: Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care* 15:815–819, 1992
145. Kohner EM, Aldington SJ, Stratton IM, Manley SE, Holman RR, Matthews DR, Turner RC: United Kingdom Prospective Diabetes Study, 30: diabetic retinopathy at diagnosis of non-insulin-dependent diabetes mellitus and associated risk factors. *Arch Ophthalmol* 116:297–303, 1998
146. Singleton JR, Smith AG, Bromberg MB: Increased prevalence of impaired glucose tolerance in patients with painful sensory neuropathy. *Diabetes Care* 24:1448–1453, 2001
147. Sumner CJ, Sheth S, Griffin JW, Cornblath DR, Polydefkis M: The spectrum of neuropathy in diabetes and impaired glucose tolerance. *Neurology* 64:108–111, 2003
148. Hara K, Shojima N, Hosoe J, Kadokawa T: Genetic architecture of type 2 diabetes. *Biochem Biophys Res Commun* 452:213–220, 2014
149. Vassy JL, Meigs JB: Is genetic testing useful to predict type 2 diabetes? *Best Pract Res Clin Endocrinol Metab* 26:189–201, 2012
150. Pradas-Juni M, Nicod N, Fernandez-Rebolledo E, Gomis R: Differential transcriptional and posttranslational transcription factor 7-like regulation among nondiabetic individuals and type 2 diabetic patients. *Mol Endocrinol* 28:1558–1570, 2014
151. Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D; Diabetes Prevention Program Research Group: TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N Engl J Med* 355:241–250, 2006
152. Walford GA, Green T, Neale B, Isakova T, Rotter JL, Grant SF, Fox CS, Pankow JS, Wilson JG, Meigs JB, Siscovick DS, Bowden DW, Daly MJ, Florez JC: Common genetic variants differentially influence the transition from clinically defined states of fasting glucose metabolism. *Diabetologia* 55:331–339, 2012
153. Genuth S, Kahn R: A step backward—or is it forward? *Diabetes Care* 31:1093–1096, 2008
154. Tirosh A, Shai I, Tekes-Manova D, Israeli E, Pereg D, Shochat T, Kochba I, Rudich A; Israeli Diabetes Research Group: Normal fasting plasma glucose levels and type 2 diabetes in young men. *N Engl J Med* 353:1454–1462, 2005

155. Abdul-Ghani MA, Williams K, DeFronzo R, Stern M: Risk of progression to type 2 diabetes based on relationship between postload plasma glucose and fasting plasma glucose. *Diabetes Care* 29:1613–1618, 2006
156. Abdul-Ghani MA, Tripathy D, DeFronzo RA: Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. *Diabetes Care* 29:1130–1139, 2006
157. Davies MJ, Raymond NT, Day JL, Hales CN, Burden AC: Impaired glucose tolerance and fasting hyperglycaemia have different characteristics. *Diabet Med* 17:433–440, 2000
158. Kanat M, Mari A, Norton L, Winnier D, DeFronzo RA, Jenkinson C, Abdul-Ghani MA: Distinct β -cell defects in impaired fasting glucose and impaired glucose tolerance. *Diabetes* 61:447–453, 2012
159. Faerch K, Borch-Johnsen K, Holst JJ, Vaag A: Pathophysiology and aetiology of impaired fasting glycaemia and impaired glucose tolerance: does it matter for prevention and treatment of type 2 diabetes? *Diabetologia* 52:1714–1723, 2009
160. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, Yazdi H, Booker L: Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. *Diabetes Res Clin Pract* 78:305–312, 2007
161. The DECODE Study Group; European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 354:617–621, 1999
162. Mooy JM, Grootenhuis PA, de Vries H, Kostense PJ, Popp-Snijders C, Bouter LM, Heine RJ: Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 39:298–305, 1996
163. James C, Bullard KM, Rolka DB, Geiss LS, Williams DE, Cowie CC, Albright A, Gregg EW: Implications of alternative definitions of prediabetes for prevalence in U.S. adults. *Diabetes Care* 34:387–391, 2011
164. Bullard KM, Saydah SH, Imperatore G, Cowie CC, Gregg EW, Geiss LS, Cheng YJ, Rolka DB, Williams DE, Caspersen CJ: Secular changes in U.S. prediabetes prevalence defined by hemoglobin A1c and fasting plasma glucose: National Health and Nutrition Examination Surveys, 1999–2010. *Diabetes Care* 36:2286–2293, 2013
165. Ford ES, Zhao G, Li C: Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol* 55:1310–1317, 2010
166. Wingard DL, Barrett-Connor EL, Scheidt-Nave C, McPhillips JB: Prevalence of cardiovascular and renal complications in older adults with normal or impaired glucose tolerance or NIDDM. A population-based study. *Diabetes Care* 16:1022–1025, 1993
167. Edelstein SL, Knowler WC, Bain RP, Andres R, Barrett-Connor EL, Dowse GK, Haffner SM, Pettitt DJ, Sorkin JD, Muller DC, Collins VR, Hamman RF: Predictors of progression from impaired glucose tolerance to NIDDM: an analysis of six prospective studies. *Diabetes* 46:701–710, 1997
168. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
169. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
170. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
171. Diabetes Prevention Program Research Group: Effects of withdrawal from metformin on the development of diabetes in the diabetes prevention program. *Diabetes Care* 26:977–980, 2003
172. Katula JA, Vitolins MZ, Rosenberger EL, Blackwell CS, Morgan TM, Lawlor MS, Goff DC, Jr.: One-year results of a community-based translation of the Diabetes Prevention Program: Healthy-Living Partnerships to Prevent Diabetes (HELP PD) Project. *Diabetes Care* 34:1451–1457, 2011
173. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
174. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
175. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51:2796–2803, 2002
176. Eriksson JG, Lehtovirta M, Ehrnstrom B, Salmela S, Groop L: Long-term beneficial effects of glipizide treatment on glucose tolerance in subjects with impaired glucose tolerance. *J Intern Med* 259:553–560, 2006
177. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Diaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Ryden LE, Yusuf S: Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med* 367:319–328, 2012
178. Crandall JP, Knowler WC, Kahn SE, Marrero D, Florez JC, Bray GA, Haffner SM, Hoskin M, Nathan DM; Diabetes Prevention Program Research Group: The prevention of type 2 diabetes. *Nat Clin Pract Endocrinol Metab* 4:382–393, 2008
179. Perreault L, Kahn SE, Christoppi CA, Knowler WC, Hamman RF; Diabetes Prevention Program Research Group: Regression from pre-diabetes to normal glucose regulation in the diabetes prevention program. *Diabetes Care* 32:1583–1588, 2009
180. Abdul-Ghani MA, Williams K, DeFronzo RA, Stern M: What is the best predictor of future type 2 diabetes? *Diabetes Care* 30:1544–1548, 2007
181. Abdul-Ghani MA, Abdul-Ghani T, Ali N, DeFronzo RA: One-hour plasma glucose concentration and the metabolic syndrome identify subjects at high risk for future type 2 diabetes. *Diabetes Care* 31:1650–1655, 2008

182. Olefsky JM, Reaven GM: Insulin and glucose responses to identical oral glucose tolerance tests performed forty-eight hours apart. *Diabetes* 23:449–453, 1974
183. Yeboah J, Bertoni AG, Herrington DM, Post WS, Burke GL: Impaired fasting glucose and the risk of incident diabetes mellitus and cardiovascular events in an adult population: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 58:140–146, 2011
184. Wang H, Shara NM, Calhoun D, Umans JG, Lee ET, Howard BV: Incidence rates and predictors of diabetes in those with prediabetes: the Strong Heart Study. *Diabetes Metab Res Rev* 26:378–385, 2010
185. Forouhi NG, Luan J, Hennings S, Wareham NJ: Incidence of type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990–2000. *Diabet Med* 24:200–207, 2007
186. Schottker B, Raum E, Rothenbacher D, Muller H, Brenner H: Prognostic value of haemoglobin A1c and fasting plasma glucose for incident diabetes and implications for screening. *Eur J Epidemiol* 26:779–787, 2011
187. Bonora E, Kiechl S, Willeit J, Oberholzer F, Egger G, Meigs JB, Bonadonna RC, Muggeo M; Bruneck Study: Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. *Diabetes* 53:1782–1789, 2004
188. Valdes S, Botas P, Delgado E, Alvarez F, Cadorniga FD: Population-based incidence of type 2 diabetes in northern Spain: the Asturias Study. *Diabetes Care* 30:2258–2263, 2007
189. Inoue K, Matsumoto M, Akimoto K: Fasting plasma glucose and HbA1c as risk factors for type 2 diabetes. *Diabet Med* 25:1157–1163, 2008
190. Heianza Y, Hara S, Arase Y, Saito K, Fujiwara K, Tsuji H, Kodama S, Hsieh SD, Mori Y, Shimano H, Yamada N, Kosaka K, Sone H: HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet* 378:147–155, 2011
191. Harati H, Hadaegh F, Tohidi M, Azizi F: Impaired fasting glucose cutoff value of 5.6 mmol/l combined with other cardiovascular risk markers is a better predictor for incident type 2 diabetes than the 6.1 mmol/l value: Tehran lipid and glucose study. *Diabetes Res Clin Pract* 85:90–95, 2009
192. Borch-Johnsen K, Colagiuri S, Balkau B, Glumer C, Carstensen B, Ramachandran A, Dong Y, Gao W: Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia* 47:1396–1402, 2004
193. Inoue K, Inoue M, Matsumoto M, Akimoto K: Persistent fasting hyperglycaemia is more predictive of type 2 diabetes than transient fasting hyperglycaemia. *Diabet Med* 29:e75–e81, 2012
194. Abdul-Ghani MA, Stern MP, Lyssenko V, Tuomi T, Groop L, DeFronzo RA: Minimal contribution of fasting hyperglycemia to the incidence of type 2 diabetes in subjects with normal 2-h plasma glucose. *Diabetes Care* 33:557–561, 2010
195. Cheng P, Neugard B, Foulis P, Conlin PR: Hemoglobin A1c as a predictor of incident diabetes. *Diabetes Care* 34:610–615, 2011
196. Chamnan P, Simmons RK, Forouhi NG, Luben RN, Khaw KT, Wareham NJ, Griffin SJ: Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the European prospective investigation of cancer-Norfolk cohort: implications for preventive strategies. *Diabetes Care* 34:950–956, 2011
197. Bonora E, Kiechl S, Mayr A, Zoppini G, Targher G, Bonadonna RC, Willeit J: High-normal HbA1c is a strong predictor of type 2 diabetes in the general population. *Diabetes Care* 34:1038–1040, 2011
198. Choi SH, Kim TH, Lim S, Park KS, Jang HC, Cho NH: Hemoglobin A1c as a diagnostic tool for diabetes screening and new-onset diabetes prediction: a 6-year community-based prospective study. *Diabetes Care* 34:944–949, 2011
199. Mann DM, Carson AP, Shimbo D, Fonseca V, Fox CS, Munther P: Impact of A1C screening criterion on the diagnosis of pre-diabetes among U.S. adults. *Diabetes Care* 33:2190–2195, 2010
200. Zhang X, Gregg EW, Williamson DF, Barker LE, Thomas W, Bullard KM, Imperatore G, Williams DE, Albright AL: A1C level and future risk of diabetes: a systematic review. *Diabetes Care* 33:1665–1673, 2010
201. Jurasic SP, Steffes MW, Miller ER 3rd, Selvin E: Alternative markers of hyperglycemia and risk of diabetes. *Diabetes Care* 35:2265–2270, 2012
202. Sato KK, Hayashi T, Harita N, Yoneda T, Nakamura Y, Endo G, Kambe H: Combined measurement of fasting plasma glucose and A1C is effective for the prediction of type 2 diabetes: the Kansai Healthcare Study. *Diabetes Care* 32:644–646, 2009
203. Okosun IS, Davis-Smith M, Paul Seale J, Ngulefac J: Applicability of a combination of hemoglobin A(1c) and fasting plasma glucose in population-based prediabetes screening. *J Diabetes* 4:407–416, 2012
204. Engelgau MM, Aubert RE, Thompson TJ, Herman WH: Screening for NIDDM in nonpregnant adults. A review of principles, screening tests, and recommendations. *Diabetes Care* 18:1606–1618, 1995
205. Engelgau MM, Narayan KM, Herman WH: Screening for type 2 diabetes. *Diabetes Care* 23:1563–1580, 2000
206. U.K. Prospective Diabetes Study Group: U.K. prospective diabetes study 16: Overview of 6 years' therapy of type II diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
207. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christoffi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM: 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 374:1677–1686, 2009
208. Zhang JX, Huang ES, Drum ML, Kirchhoff AC, Schlichting JA, Schaefer CT, Heuer LJ, Chin MH: Insurance status and quality of diabetes care in community health centers. *Am J Public Health* 99:742–747, 2009
209. Milano AF: Diabetes mellitus and life insurance. *J Insur Med* 33:50–103, 2001
210. McMahon BT, West SL, Mansouri M, Belongia L: Workplace discrimination and diabetes: the EEOC Americans with Disabilities Act research project. *Work* 25:9–18, 2005
211. Smith SL, Tessaro IA: Cultural perspectives on diabetes in an Appalachian population. *Am J Health Behav* 29:291–301, 2005
212. Della LJ: Exploring diabetes beliefs in at-risk Appalachia. *J Rural Health* 27:3–12, 2011
213. Eborall HC, Griffin SJ, Prevost AT, Kinmonth AL, French DP, Sutton S: Psychological impact of screening for type 2 diabetes: controlled trial and comparative study embedded in the ADDITION (Cambridge) randomised controlled trial. *BMJ* 335:486, 2007
214. Park P, Simmons RK, Prevost AT, Griffin SJ: Screening for type 2 diabetes is feasible, acceptable, but associated with increased short-term anxiety: a randomised controlled trial in British general practice. *BMC Public Health* 8:350, 2008

215. U.S. Preventive Services Task Force: Screening for type 2 diabetes mellitus in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 148:846–854, 2008
216. Norris SL, Kansagara D, Bougatsos C, Fu R; U.S. Preventive Services Task Force: Screening adults for type 2 diabetes: a review of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 148:855–868, 2008
217. Villarivera C, Wolcott J, Jain A, Zhang Y, Goodman C: Analysis & commentary: The US Preventive Services Task Force should consider a broader evidence base in updating its diabetes screening guidelines. *Health Aff (Millwood)* 31:35–42, 2012
218. Casagrande SS, Cowie CC, Fradkin JE: Utility of the U.S. Preventive Services Task Force criteria for diabetes screening. *Am J Prev Med* 45:167–174, 2013
219. Siu AL; U.S. Preventive Services Task Force: Screening for Abnormal Blood Glucose and Type 2 Diabetes Mellitus: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* 163:861–868, 2015
220. American Academy of Family Physicians: *AAFP Policy Action: Summary of Recommendations for Clinical Preventive Services*. Revision 6.3. March 2007. Leawood, KS: American Academy of Family Physicians, 2007
221. Feig DS, Palda VA, Lipscombe L; Canadian Task Force on Preventive Health Care: Screening for type 2 diabetes mellitus to prevent vascular complications: updated recommendations from the Canadian Task Force on Preventive Health Care. *CMAJ* 172:177–180, 2005
222. Tankova T, Chakarova N, Atanassova I, Dakovska L: Evaluation of the Finnish Diabetes Risk Score as a screening tool for impaired fasting glucose, impaired glucose tolerance and undetected diabetes. *Diabetes Res Clin Pract* 92:46–52, 2011
223. Public Health Agency of Canada: *The Canadian Diabetes Risk Assessment Questionnaire CANRISK*. Ottawa (ON): Public Health Agency of Canada, 2009. Available from archive.diabetes.ca/documents/for-professionals/NBI-CANRISK.pdf. Accessed 9 October 2014
224. Canadian Task Force on Preventive Health Care, Pottie K, Jaramillo A, Lewin G, Dickinson J, Bell N, Brauer P, Dunfield L, Joffres M, Singh H, Tonelli M: Recommendations on screening for type 2 diabetes in adults. *CMAJ* 184:1687–1696, 2012
225. World Health Organization: *Screening for Type 2 Diabetes. Report of a World Health Organization and International Diabetes Federation Meeting*. World Health Organization Department of Noncommunicable Disease Management, Geneva, 2003
226. Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, Williams R, John A: Screening for type 2 diabetes: literature review and economic modelling. *Health Technol Assess* 11:iii–iv, ix–xi, 1–125, 2007
227. Simmons RK, Rahman M, Jakes RW, Yuyun MF, Niggebrugge AR, Hennings SH, Williams DR, Wareham NJ, Griffin SJ: Effect of population screening for type 2 diabetes on mortality: long-term follow-up of the Ely cohort. *Diabetologia* 54:312–319, 2011
228. Rahman M, Simmons RK, Hennings SH, Wareham NJ, Griffin SJ: How much does screening bring forward the diagnosis of type 2 diabetes and reduce complications? Twelve year follow-up of the Ely cohort. *Diabetologia* 55:1651–1659, 2012
229. Selph S, Dana T, Blazina I, Bougatsos C, Patel H, Chou R: Screening for type 2 diabetes mellitus: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 162:765–776, 2015
230. O'Connor PJ, Rush WA, Cherney LM, Pronk NP: Screening for diabetes mellitus in high-risk patients: cost, yield, and acceptability. *Eff Clin Pract* 4:271–277, 2001
231. Tabaei BP, Engelgau MM, Herman WH: A multivariate logistic regression equation to screen for dysglycaemia: development and validation. *Diabet Med* 22:599–605, 2005
232. American Diabetes Association: American diabetes alert. *Diabetes Forecast* 46:54–55, 1993
233. Burden ML, Burden AC: The American Diabetes Association screening questionnaire for diabetes. Is it worthwhile in the U.K.? *Diabetes Care* 17:97, 1994
234. Silverman RA, Thakker U, Ellman T, Wong I, Smith K, Ito K, Graff K: Hemoglobin A1c as a screen for previously undiagnosed prediabetes and diabetes in an acute-care setting. *Diabetes Care* 34:1908–1912, 2011
235. Kilmer G, Hughes E, Zhang X, Elam-Evans L: Diabetes and prediabetes: screening and prevalence among adults with coronary heart disease. *Am J Prev Med* 40:159–165, 2011
236. Silbernagel G, Kleber ME, Grammer TB, Winkelmann BR, Boehm BO, Marz W: Additional use of glycated hemoglobin for diagnosis of type 2 diabetes in people undergoing coronary angiography reveals a subgroup at increased cardiovascular risk. *Diabetes Care* 34:2471–2473, 2011
237. Hasdai D, Granger CB, Srivatsa SS, Criger DA, Ellis SG, Califf RM, Topol EJ, Holmes DR, Jr.: Diabetes mellitus and outcome after primary coronary angioplasty for acute myocardial infarction: lessons from the GUSTO-IIb Angioplasty Substudy. *Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes. J Am Coll Cardiol* 35:1502–1512, 2000
238. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 335:217–225, 1996
239. Luisa BN, Roy G, Kawano J, Schrader R: Glycosylated hemoglobin for diagnosis of prediabetes in acute ischemic stroke patients. *J Stroke Cerebrovasc Dis* 22:e564–e567, 2013
240. AlGhamdi AS, Merdad K, Sonbul H, Bukhari SM, Elias WY: Dental clinics as potent sources for screening undiagnosed diabetes and prediabetes. *Am J Med Sci* 345:331–334, 2013
241. Coutinho M, Gerstein HC, Wang Y, Yusuf S: The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care* 22:233–240, 1999
242. Smith NL, Barzilay JI, Shaffer D, Savage PJ, Heckbert SR, Kuller LH, Kronmal RA, Resnick HE, Psaty BM: Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. *Arch Intern Med* 162:209–216, 2002
243. Hoogwerf BJ, Sprecher DL, Pearce GL, Acevedo M, Frolikis JP, Foody JM, Cross JA, Pashkow FJ, Robinson K, Vida DG: Blood glucose concentrations < or = 125 mg/dl and coronary heart disease risk. *Am J Cardiol* 89:596–599, 2002
244. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N: Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med* 141:413–420, 2004
245. Sorkin JD, Muller DC, Fleg JL, Andres R: The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 28:2626–2632, 2005
246. Groeneveld Y, Petri H, Hermans J, Springer MP: Relationship between blood glucose level and mortality in type 2 diabetes mellitus: a systematic review. *Diabet Med* 16:2–13, 1999

247. DECODE Study Group; The European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–404, 2001
248. Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, Zagar T, Poole CD: Survival as a function of HbA1c) in people with type 2 diabetes: a retrospective cohort study. *Lancet* 375:481–489, 2010
249. Saydah S, Tao M, Imperatore G, Gregg E: GHb level and subsequent mortality among adults in the U.S. *Diabetes Care* 32:1440–1446, 2009
250. Selvin E, Steffes MW, Zhu H, Matsushita K, Wagenknecht L, Pankow J, Coresh J, Brancati FL: Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. *N Engl J Med* 362:800–811, 2010
251. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC, Jr., Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH, Jr., Probstfield JL, Simons-Morton DG, Friedewald WT: Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 358:2545–2559, 2008
252. ACCORD Study Group, Gerstein HC, Miller ME, Genuth S, Ismail-Beigi F, Buse JB, Goff DC, Jr., Probstfield JL, Cushman WC, Ginsberg HN, Bigger JT, Grimm RH, Jr., Byington RP, Rosenberg YD, Friedewald WT: Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 364:818–828, 2011
253. Duckworth W, Abraira C, Moritz T, Reda D, Emanuele N, Reaven PD, Zieve FJ, Marks J, Davis SN, Hayward R, Warren SR, Goldman S, McCarren M, Vitek ME, Henderson WG, Huang GD; VADT Investigators: Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 360:129–139, 2009
254. ADVANCE Collaborative Group, Patel A, MacMahon S, Chalmers J, Neal B, Billot L, Woodward M, Marre M, Cooper M, Glasziou P, Grobbee D, Hamet P, Harrap S, Heller S, Liu L, Mancia G, Mogensen CE, Pan C, Poulter N, Rodgers A, Williams B, Bompastor S, de Galan BE, Joshi R, Travert F: Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 358:2560–2572, 2008
255. Gerstein HC, Miller ME, Ismail-Beigi F, Largay J, McDonald C, Lochner HA, Booth GL; ACCORD Study Group: Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. *Lancet* 384:1936–1941, 2014
256. Sandbaek A, Griffin SJ, Rutten G, Davies M, Stolk R, Khunti K, Borch-Johnsen K, Wareham NJ, Lauritzen T: Stepwise screening for diabetes identifies people with high but modifiable coronary heart disease risk. The ADDITION study. *Diabetologia* 51:1127–1134, 2008
257. Stevens RJ, Kothari V, Adler AI, Stratton IM; United Kingdom Prospective Diabetes Study (UKPDS) Group: The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 101:671–679, 2001
258. Griffin SJ, Borch-Johnsen K, Davies MJ, Khunti K, Rutten GE, Sandbæk A, Sharp SJ, Simmons RK, van den Donk M, Wareham NJ, Lauritzen T: Effect of early intensive multifactorial therapy on 5-year cardiovascular outcomes in individuals with type 2 diabetes detected by screening (ADDITION-Europe): a cluster-randomised trial. *Lancet* 378:156–167, 2011
259. Sandbæk A, Griffin SJ, Sharp SJ, Simmons RK, Borch-Johnsen K, Rutten GE, van den Donk M, Wareham NJ, Lauritzen T, Davies MJ, Khunti K: Effect of early multifactorial therapy compared with routine care on microvascular outcomes at 5 years in people with screen-detected diabetes: a randomized controlled trial: the ADDITION-Europe Study. *Diabetes Care* 37:2015–2023, 2014
260. Simmons RK, Echouffo-Tcheugui JB, Sharp SJ, Sergeant LA, Williams KM, Prevost AT, Kinmonth AL, Wareham NJ, Griffin SJ: Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): a cluster-randomised controlled trial. *Lancet* 380:1741–1748, 2012
261. Li G, Zhang P, Wang J, An Y, Gong Q, Gregg EW, Yang W, Zhang B, Shuai Y, Hong J, Engelgau MM, Li H, Roglic G, Hu Y, Bennett PH: Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol* 2:474–480, 2014
262. American Diabetes Association: Screening for type 2 diabetes. *Diabetes Care* 27(Suppl 1):S11–S14, 2004
263. American Diabetes Association: Standards of medical care in diabetes—2014. *Diabetes Care* 37 (Suppl 1):S14–S80, 2014
264. Casagrande SS, Cowie CC, Genuth SM: Self-reported prevalence of diabetes screening in the U.S., 2005–2010. *Am J Prev Med* 47:780–787, 2014
265. Rolka DB, Narayan KM, Thompson TJ, Goldman D, Lindenmayer J, Alich K, Bacall D, Benjamin EM, Lamb B, Stuart DO, Engelgau MM: Performance of recommended screening tests for undiagnosed diabetes and dysglycemia. *Diabetes Care* 24:1899–1903, 2001
266. Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB: A new look at screening and diagnosing diabetes mellitus. *J Clin Endocrinol Metab* 93:2447–2453, 2008
267. Wang W, Lee ET, Fabsitz R, Welty TK, Howard BV: Using HbA1c to improve efficacy of the American Diabetes Association fasting plasma glucose criterion in screening for new type 2 diabetes in American Indians: the Strong Heart Study. *Diabetes Care* 25:1365–1370, 2002
268. Ko GT, Chan JC, Yeung VT, Chow CC, Tsang LW, Li JK, So WY, Wai HP, Cockram CS: Combined use of a fasting plasma glucose concentration and HbA1c or fructosamine predicts the likelihood of having diabetes in high-risk subjects. *Diabetes Care* 21:1221–1225, 1998
269. Hajat C, Harrison O, Al Siksek Z: Diagnostic testing for diabetes using HbA1c) in the Abu Dhabi population: Weqaya: the Abu Dhabi cardiovascular screening program. *Diabetes Care* 34:2400–2402, 2011
270. Rohlfing CL, Little RR, Wiedmeyer HM, England JD, Madsen R, Harris MI, Flegal KM, Eberhardt MS, Goldstein DE: Use of GHb (HbA1c) in screening for undiagnosed diabetes in the U.S. population. *Diabetes Care* 23:187–191, 2000
271. Bennett CM, Guo M, Dharmage SC: HbA1c as a screening tool for detection of type 2 diabetes: a systematic review. *Diabet Med* 24:333–343, 2007
272. Bianchi C, Miccoli R, Bonadonna RC, Giorgino F, Frontoni S, Faloria E, Marchesini G, Dolci MA, Cavalot F, Cavallo GM, Leonetti F, Del Prato S; GENFIEV Investigators: Pathogenetic mechanisms and cardiovascular risk: differences between HbA1c and oral glucose tolerance test for the diagnosis of glucose tolerance. *Diabetes Care* 35:2607–2612, 2012
273. Clarke PM, Gray AM, Briggs A, Stevens RJ, Matthews DR, Holman RR; UKPDS 72 United Kingdom Prospective Diabetes Study: Cost-utility analyses of intensive blood glucose and tight blood pressure control in type 2 diabetes (UKPDS 72). *Diabetologia* 48:868–877, 2005

274. Clarke P, Gray A, Adler A, Stevens R, Raikou M, Cull C, Stratton I, Holman R; UKPDS Group: United Kingdom Prospective Diabetes Study: Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type II diabetes (UKPDS No. 51). *Diabetologia* 44:298–304, 2001
275. Clarke P, Gray A, Legood R, Briggs A, Holman R: The impact of diabetes-related complications on healthcare costs: results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65). *Diabet Med* 20:442–450, 2003
276. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE; Diabetes Prevention Program Research Group: The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 142:323–332, 2005
277. Herman WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, Lachin JM, Engelgau MM; Diabetes Prevention Program Research Group: Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care* 26:36–47, 2003
278. Diabetes Prevention Program Research Group: The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPoS. *Diabetes Care* 35:723–730, 2012
279. Eastman RC, Javitt JC, Herman WH, Dasbach EJ, Copley-Merriman C, Maier W, Dong F, Manninen D, Zbrozek AS, Kotsanos J, Garfield SA, Harris M: Model of complications of NIDDM. II. Analysis of the health benefits and cost-effectiveness of treating NIDDM with the goal of normoglycemia. *Diabetes Care* 20:735–744, 1997
280. Kahn R, Alperin P, Eddy D, Borch-Johnsen K, Buse J, Feigelman J, Gregg E, Holman RR, Kirkman MS, Stern M, Tuomilehto J, Wareham NJ: Age at initiation and frequency of screening to detect type 2 diabetes: a cost-effectiveness analysis. *Lancet* 375:1365–1374, 2010
281. Hoerger TJ, Harris R, Hicks KA, Donahue K, Sorensen S, Engelgau M: Screening for type 2 diabetes mellitus: a cost-effectiveness analysis. *Ann Intern Med* 140:689–699, 2004
282. Zhang P, Engelgau MM, Valdez R, Benjamin SM, Cadwell B, Narayan KM: Costs of screening for pre-diabetes among US adults: a comparison of different screening strategies. *Diabetes Care* 26:2536–2542, 2003
283. Slade AN: Health investment decisions in response to diabetes information in older Americans. *J Health Econ* 31:502–520, 2012
284. Kahn ME: Education's role in explaining diabetic health investment differentials. *Econ Educ Rev* 17:257–266, 1998
285. Griffin SJ, Simmons RK, Prevost AT, Williams KM, Hardeman W, Sutton S, Brage S, Ekelund U, Parker RA, Wareham NJ, Kinmonth AL; ADDITION-Plus study team: Multiple behaviour change intervention and outcomes in recently diagnosed type 2 diabetes: the ADDITION-Plus randomised controlled trial. *Diabetologia* 57:1308–1319, 2014
286. Long GH, Cooper AJ, Wareham NJ, Griffin SJ, Simmons RK: Healthy behavior change and cardiovascular outcomes in newly diagnosed type 2 diabetic patients: a cohort analysis of the ADDITION-Cambridge study. *Diabetes Care* 37:1712–1720, 2014
287. Geiss LS, James C, Gregg EW, Albright A, Williamson DF, Cowie CC: Diabetes risk reduction behaviors among U.S. adults with prediabetes. *Am J Prev Med* 38:403–409, 2010
288. Vehik K, Beam CA, Mahon JL, Schatz DA, Haller MJ, Sosenko JM, Skyler JS, Krischer JP; TrialNet Natural History Study Group: Development of autoantibodies in the TrialNet Natural History Study. *Diabetes Care* 34:1897–1901, 2011
289. Yu L, Boulware DC, Beam CA, Hutton JC, Wenzlau JM, Greenbaum CJ, Bingley PJ, Krischer JP, Sosenko JM, Skyler JS, Eisenbarth GS, Mahon JL; Type 1 Diabetes TrialNet Study Group: Zinc transporter-8 autoantibodies improve prediction of type 1 diabetes in relatives positive for the standard biochemical autoantibodies. *Diabetes Care* 35:1213–1218, 2012
290. Sosenko JM, Skyler JS, Mahon J, Krischer JP, Beam CA, Boulware DC, Greenbaum CJ, Rafkin LE, Cowie C, Cuthbertson D, Palmer JP; Type 1 Diabetes TrialNet Study Group; Diabetes Prevention Trial-Type 1 Study Group: The application of the diabetes prevention trial-type 1 risk score for identifying a preclinical state of type 1 diabetes. *Diabetes Care* 35:1552–1555, 2012
291. Werner EF, Pettker CM, Zuckerwise L, Reel M, Funai EF, Henderson J, Thung SF: Screening for gestational diabetes mellitus: are the criteria proposed by the international association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care* 35:529–535, 2012
292. HAPO Study Cooperative Research Group, Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA: Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 358:1991–2002, 2008
293. Lee KF, Mak MW, Lau KO, Chung HH: Risk of development of diabetes mellitus in Chinese women with persistently impaired glucose tolerance after gestational diabetes. *Hong Kong Med J* 17:195–201, 2011