Diagnosis and Management of Type 2 Diabetes

Fourteenth Edition

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Diabetes Statistics

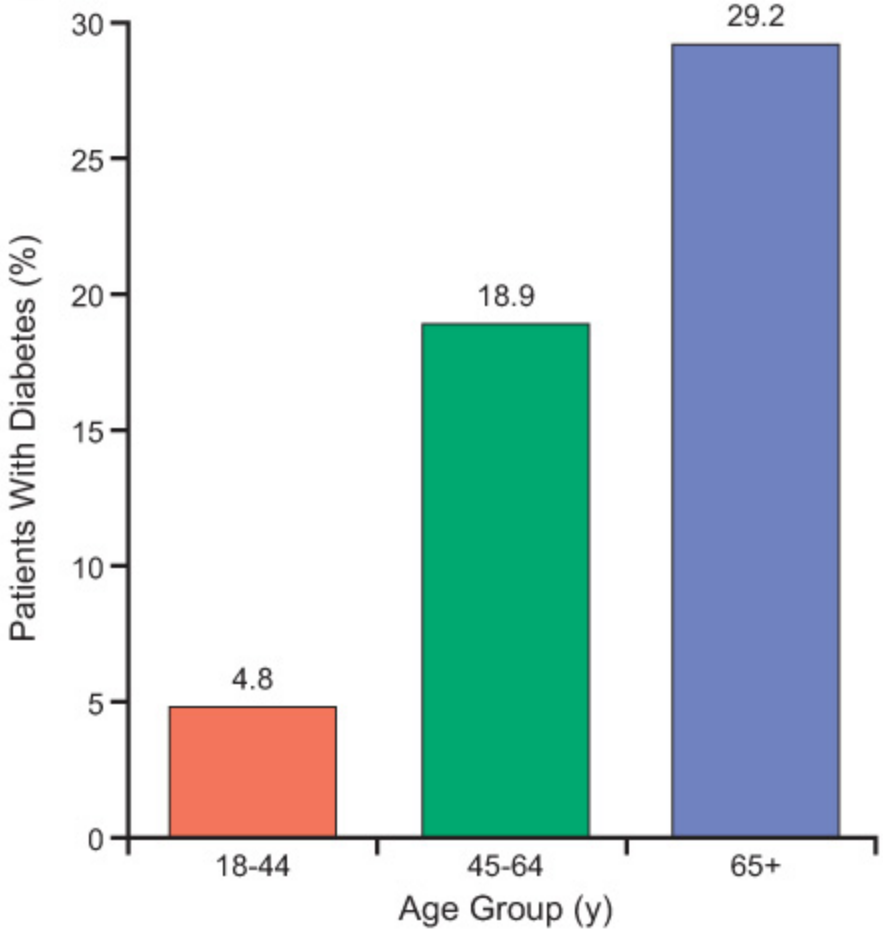
The prevalence of type 2 diabetes (T2D) is increasing, not only in the United States, but also around the world. Diabetes affects approximately 537 million people worldwide and is expected to affect 783 million by 2045. The prevalence of diabetes refers to the total number of people known to have the disease at a particular time. In 2017-2020, approximately 37.3 million Americans (11.3% of the US population) had diabetes, with a higher rate of prevalence in certain geographic areas, and approximately one in four of those individuals (23.0%) were estimated to have undiagnosed diabetes. The prevalence has increased from 4.9% in 1990 to 11.3% in 2017-2020. Possible reasons for the substantial increases in the prevalence of diabetes over time include:

- Advancing age of the US population
- Reduced mortality rates among people with diabetes due to improved screening, detection, and health care
- An increase in risk factors, such as obesity and physical inactivity.

The prevalence of diabetes increases with advancing age, reaching nearly 29.2% for those in the age category of ≥65 years (**Figure 1.1**). The prevalence is similar for men and women up to the age of 65; for those over 65, the prevalence rates are slightly higher for men.

The prevalence of individuals with T2D is considerably different depending on the race, ethnicity, and gender in the US population. Diabetes is more prevalent in American Indians, Alaska natives, Hispanics and Latinos, and non-Hispanic blacks (**Figure 1.2**). The increasing number of ethnic/racial minorities in the United States may also contribute to the increasing prevalence of T2D.

FIGURE 1.1 — Estimated Percentage of Diagnosed and Undiagnosed Diabetes Among Adults Aged ≥18 Years, United States, 2017-2020



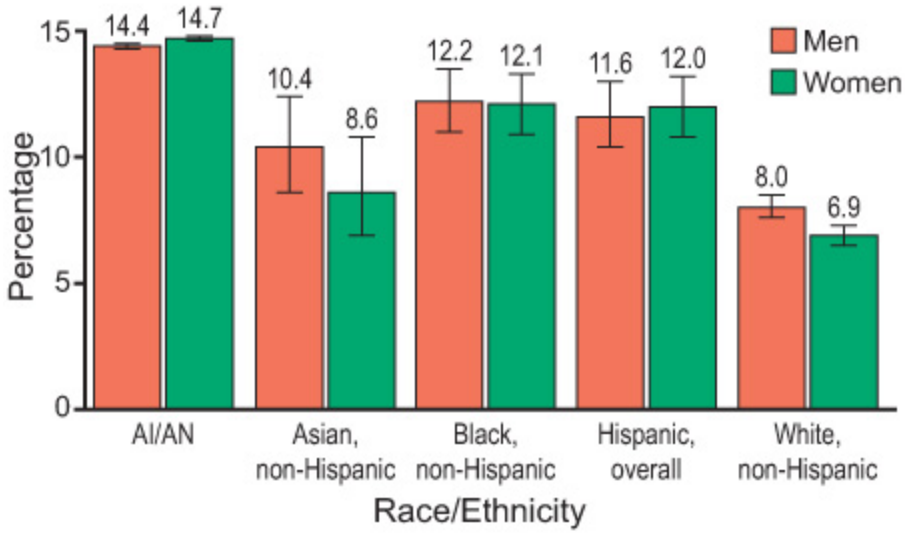
National Diabetes Statistics Report, 2022. CDC Web site. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed May 9, 2022.

The lowering of the clinical diagnostic criteria for diabetes from a fasting blood glucose (FBG) of 140 mg/dL to 126 mg/dL has also contributed to the higher prevalence of diabetes. Ethnic and racial minorities not only have a higher prevalence of diabetes, but they also account for a greater number of individuals with undiagnosed diabetes as well as prediabetes, which is a major risk factor for the development of T2D.

Undiagnosed T2D is a serious problem. The prevalence rate of undiagnosed diabetes increases with age in both men and women. In 2019,

approximately 8.5 million people were estimated to have undiagnosed diabetes. An estimated 38.0% of US adults aged 18 years or older had prediabetes in 2017-2020 based on their fasting glucose or A1C level. The estimated percentage of prediabetes among adults aged 18 years and older is shown in **Figure 1.3**.

FIGURE 1.2 — Estimated Age-Adjusted Prevalence of Diagnosed Diabetes by Race-Ethnicity and Sex Among Adults Aged ≥18 Years, United States, 2018-2019



Key: AI/AN, American Indian/Alaska Native.

Error bars represent upper and lower bounds of the 95% confidence interval.

Data source: 2018–2019 National Health Interview Survey; 2019 Indian Health Service National Data Warehouse (for American Indian/Alaska Native group only).

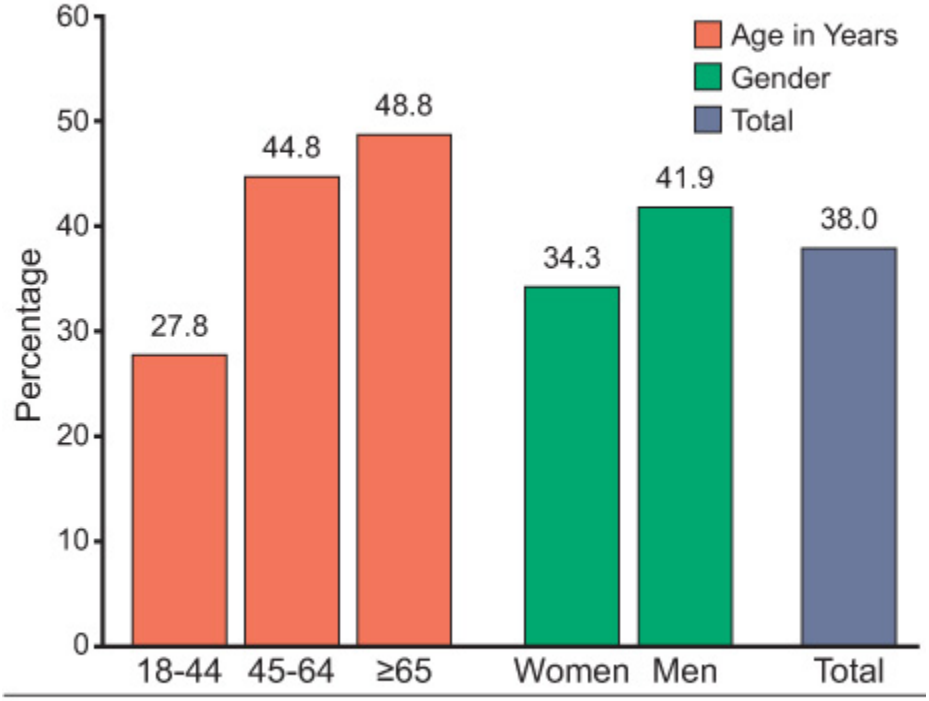
National Diabetes Statistics Report, 2022. CDC Web site. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed May 9, 2022.

Insulin resistance and the associated macrovascular complications are well known to develop 10 to 15 years before the typical diagnosis of T2D, because of the asymptomatic nature of T2D, especially in the early stages. In the United Kingdom Prospective Diabetes Study (UKPDS), 21% of newly diagnosed diabetics already had diabetic retinopathy. Since diabetic

retinopathy requires at least 4 to 7 years of hyperglycemia to develop, this indicates that diabetes had likely been undiagnosed for this period of time. In addition, these newly diagnosed subjects also had a two to three times higher incidence of myocardial infarction (MI) and stroke compared with the general population. The UKPDS data are from over 2 decades ago but unfortuately have not changed much in recent years.

The incidence of diabetes is the number of new cases diagnosed during a certain period of time, usually within the previous year. In 2019, approximately 1.4 million adults aged 18 years and older were newly diagnosed with diabetes.

FIGURE 1.3 — Estimated Percentage of Prediabetes Among Adults Aged ≥18 Years, United States, 2017-2020



Adapted from National Diabetes Statistics Report, 2022. CDC Web site. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed May 9, 2022.

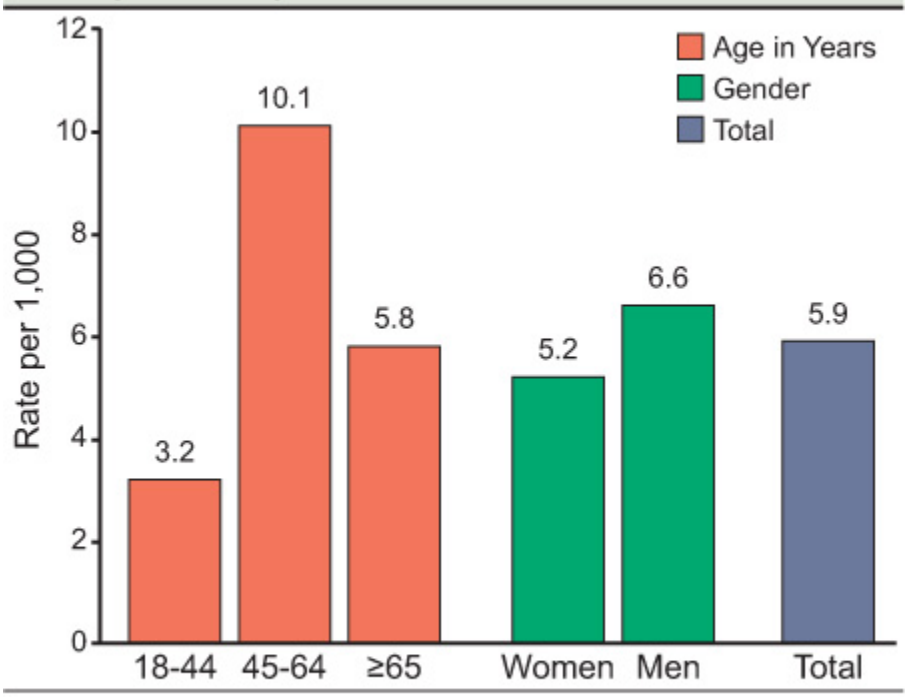
From 1980 through 2015, the incidence of diagnosed diabetes was lower among adults aged 18 to 44 years compared with older age groups. During this period, the incidence of diagnosed diabetes increased among

adults aged 18 to 44 years and 65 to 79 years. Among adults 45 to 64 years, the incidence of diagnosed diabetes showed little change during the 1980s but increased beginning in the 1990s through 2015. However, the overall incidence rates have shown a decreasing trend in the period 2008-2019. The estimated incidence of diabetes among adult aged ≥18 years in the United States in 2018-2019 is shown in **Figure 1.4**.

In a similar fashion to prevalence, the incidence rates for African Americans, Latinos, American Indians, Pacific Islanders, and Asian Indians are higher than for Whites.

Some experts believe that the high incidence of diabetes is due to a genetic predisposition to diabetes commonly referred to as "the thrifty gene hypothesis," which theorizes that in the distant past, most individuals were hunters and gatherers doing physical labor for their daily existence. In times of famine, any individual who was not thin and had insulin resistance would be in a prime position to survive and not perish from starvation during periods of drought. In a relatively short period of time, individuals in our westernized societies are doing less physical labor, growing older, becoming much more obese, and consuming foods in greater amounts and with a much higher percentage of fat. What was a physiologic advantage in the past is now a physiologic disadvantage. All of these factors are thought to contribute to the increasing incidence of T2D over the centuries.

FIGURE 1.4 — Estimated Incidence of Diabetes Among Adults Aged ≥18 Years, United States, 2018-2019



Adapted from National Diabetes Statistics Report, 2022. CDC Web site. https://www.cdc.gov/diabetes/data/statistics-report/index.html. Accessed May 9, 2022.

In conclusion, diabetes has achieved or is nearing epidemic proportions in many ethnic groups, not only in the United States, but also in other populations around the globe. Diabetes was the eighth leading cause of death in the United States in 2020. Much of the increase is due to our westernized society and lifestyle, in addition to genetic influences, which contribute significantly to the overall morbidity and mortality associated with the presence of T2D. Overall, the risk of death for people with diabetes is about two times that of people without diabetes. In order to reduce the emotional and physical suffering of people with T2D, a concerted effort should be undertaken toward the prevention, early detection, and aggressive management of this devastating medical condition.

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Pathophysiology and Natural History

Pathophysiology

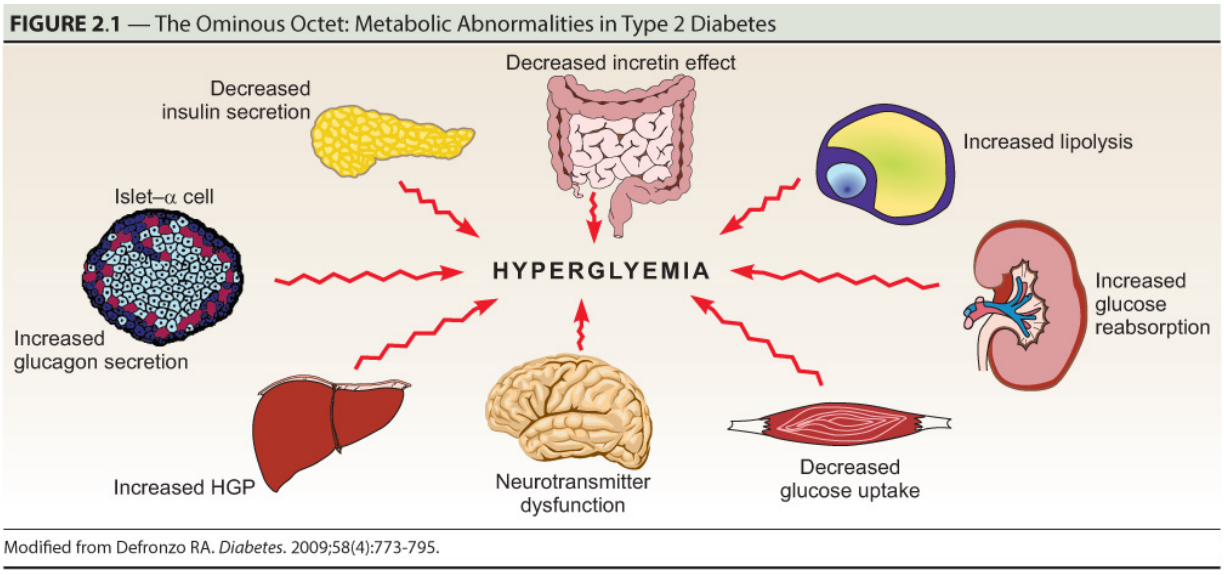
Type 2 diabetes is known to have a strong genetic component with contributing environmental determinants. The genetic influence is readily apparent from data of twin and family studies. Identification of T2D susceptibility genes has been elusive, and investigation of a number of candidate genes has been largely negative, yielding a very small population of patients (<5%) with genetic variation in any of the candidate genes studied to date.

It is likely that no single genetic defect will emerge to explain T2D; thus, the disease is heterogeneous, probably multigenic, and likely has a complex etiology. Even though the disease is genetically heterogeneous, there appears to be a fairly consistent phenotype once the disease is fully manifest. Most patients with T2D and fasting hyperglycemia are characterized by:

- Peripheral insulin resistance, mainly in the skeletal muscle but also in the liver and adipose tissue
- Impaired insulin secretion by the pancreas
- Excessive glucose production by the liver.

Although these three metabolic abnormalities have been well studied and characterized, the etiologic sequence has now come into focus. In addition to these three classic defects, there has been a plethora of additional metabolic and hormonal abnormalities identified as newer pharmacologic agents have been developed for the treatment of T2D. As shown in **Figure 2.1**, five additional defects have been identified, including:

- Excessive glucagon secretion
- Increased glucose reabsorption by the kidney
- Neurotransmitter dysfunction
- Accelerated lipolysis in fat cells
- Decreased incretin effect.



It is probable that the increased hepatic glucose production of T2D is secondary and can be fully reversed with a variety of forms of antidiabetic therapy. In addition, increased hepatic glucose production rates are not major contributors to prediabetes. This leaves insulin resistance, impaired insulin secretion, or both, as initiating abnormalities.

Accumulated evidence strongly supports the idea that both insulin resistance and impaired insulin secretion precede the onset of hyperglycemia and the T2D phenotype. However, insulin resistance is quantitatively more severe in the prediabetic phenotype. In fact, studies have also shown that insulin secretion, including first-phase insulin responses to intravenous (IV) glucose, are either normal or quantitatively increased in the prediabetic state. Thus, substantial evidence from the literature indicates that those individuals who evolve from prediabetes to T2D begin with significant insulin resistance.

Although genetic factors underlie the etiology of T2D in most patients, acquired factors are also likely to be contributory, including such factors as:

- Obesity, particularly central or visceral obesity
- Sedentary lifestyle
- High-fat diet

The aging process also contributes to the expression of T2D in genetically susceptible individuals. When the β-cell function is able to compensate for insulin resistance, hyperinsulinemia develops, which maintains relatively normal glucose tolerance. Therefore, in the compensated insulin-resistant, hyperinsulinemic state, one has either normal glucose tolerance or prediabetes, but not diabetes. A subpopulation of individuals with compensated insulin resistance eventually go on to develop T2D. The magnitude of this subpopulation depends on the methods used to detect glucose intolerance, the particular ethnic groups studied, and several other acquired and metabolic abnormalities that may be present. In addition, during the transition from the compensated state to frank T2D, at least three main pathophysiologic changes can be observed:

- First, basal hepatic glucose production rates progressively increase, which is a characteristic feature of essentially all patients with T2D with fasting hyperglycemia.
- Second, the insulin resistance usually becomes more severe, which may be due to the degree of genetic load and/or acquired conditions, such as obesity, sedentary lifestyle, and aging. Antidiabetic treatment can completely normalize the elevated hepatic glucose production rates and partially ameliorate the insulin resistance so that the degree of insulin resistance returns approximately to the level present in the IGT state.
- The third and most marked change is a decrease in β-cell function and decline in insulin secretory ability. Whether this decline in insulin secretion is because of preprogrammed genetic abnormalities in β-cell function or primarily due to acquired defects, such as glucose or metabolic toxicity, β-cell exhaustion, or both, remains to be elucidated. Nevertheless, a marked decrease in β-cell function accompanies this

transition and is thought to be a major contributor to the transition from prediabetes to T2D.

In summary, the proposed etiologic sequence is that insulin resistance and abnormalities of pancreatic insulin secretion (either or both may be genetic in origin) are manifest initially. The pancreas tries to compensate for insulin resistance, which leads to increased insulin secretion to maintain the prediabetic state. In time, the compensation fails and β-cell function declines, leading to hyperglycemia. Note, however, that most patients with T2D, particularly the majority who are obese at the time of initial diagnosis, are still hyperinsulinemic. In addition, the conversion of prediabetes to T2D can also be influenced by:

- Ethnicity and genetics
- Degree of obesity
- Distribution of body fat
- Sedentary lifestyle
- Aging
- Other concomitant medical conditions.

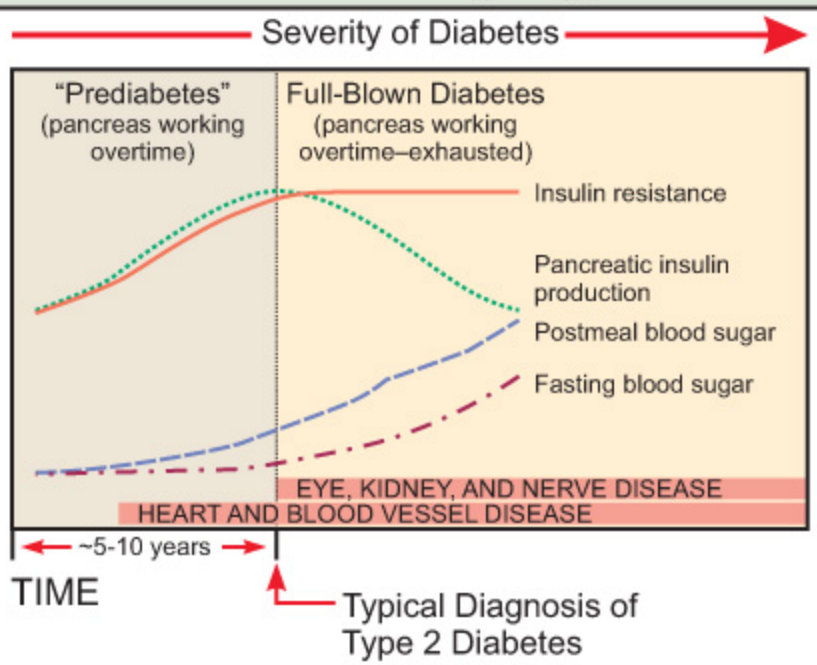
The heterogeneous nature of T2D and its natural history result in a varied response to the different antidiabetic agents over time.

The Natural History of Diabetes

Type 2 diabetes is at one end of the continuum represented by the fully compensated insulin-resistant state to prediabetes and then to frank T2D. A triad of metabolic defects characterize T2D: insulin resistance, nonautoimmune β-cell dysfunction, and inappropriately increased hepatic glucose production (**Figure 2.2**). The natural history of T2D directly reflects the interrelationships between these three defects. The primary and earliest pathogenic lesion is insulin resistance, and the β-cell is able to compensate for a variable length of time by secreting supraphysiologic amounts of insulin. Insulin resistance, compensatory hyperinsulinemia, and

mild postprandial hyperglycemia characterize prediabetes. Over time, however, the β-cell begins to fail and as relative insulin deficiency occurs, fasting hyperglycemia and full-blown T2D develops. In addition, as insulin levels fall, the inhibitory effect of insulin on hepatic glucose production decreases and significant fasting hyperglycemia develops. Further progression of the disease is marked by an absolute insulin deficiency. Obesity, aging, weight gain in adulthood, and physical inactivity are some of the environmental factors that impact the rate of development of diabetes.

FIGURE 2.2 — The Natural History of Type 2 Diabetes



Insulin resistance can be present for many years before the diagnosis of diabetes. Blood glucose levels are not markedly elevated in the early stages of diabetes. Once the pancreas becomes exhausted, blood glucose values increase dramatically. As the pancreas becomes exhausted, the chance of achieving good glucose control with diet and exercise alone or with one oral agent is reduced.

Screening patients for prediabetes is probably the best way for early identification of high-risk individuals. Screening can be performed by measurement of A1C, fasting or 2-hour plasma glucose testing after a 75-g

oral glucose load. In general clinical practice, measurement of A1C is often the preferred method of diagnosis because of convenience (fasting is not required, so it can be measured at any time of day) and greater reproducibility. However, A1C testing is more expensive and may not be available in regions of the developing world.

For asymptomatic individuals, testing for prediabetes should begin at age at age 45 or earlier in any overweight or obese adults (BMI $\geq$25 kg/m^2) with one or more additional risk factors for T2D. In individuals with normal blood glucose and/or A1C results, testing should be repeated at least every 3 years. In children and adolescents, testing for prediabetes should be considered in overweight or obese individuals with two or more additional risk factors for T2D.

Individuals meeting the criteria for prediabetes (discussed in *Chapter 3*) should be informed of their risks, and be made aware of risk-reduction strategies. The presence of IFG, IGT, and elevated A1C indicate an increased risk for other syndromes associated with insulin resistance, such as hypertension and dyslipidemia, that also require an aggressive diagnostic and therapeutic plan.

Understanding the natural history of T2D aids the clinician in identifying those patients most at risk for developing diabetes and aids in devising an effective treatment plan for those who already have the disease. Each of the available classes of oral antidiabetic agents has a different mechanism of action and is, therefore, potentially most effective at different stages in the continuum from prediabetes to frank diabetes. Given that insulin resistance is one of the major pathogenic factors in the prediabetic state and continues to persist in frank diabetes, efforts to enhance insulin sensitivity in the liver using metformin (MET) as a first-line agent are useful. Thiazolidinediones (TZD) also enhance insulin sensitivity (primarily in peripheral tissues) and are also useful in the prevention and early treatment of diabetes; however, they have fallen out of favor due to their side effect profile. Other pharmacological agents shown to reduce the incidence of diabetes include ACE inhibitors (DREAM trial), α-glucosidase inhibitors (STOP-NIDDM trial), and orlistat (XENDOS trial). Metformin is the agent with the strongest evidence base and best long-term safety profile

for the prevention of diabetes, although lifestyle changes (such as increased exercise and weight loss) are even more effective. Prevention of T2D is discussed in more detail in *Chapter 24*. Perhaps the SGLT2 inhibitor (*Chapter 11*) and GLP-1 RA (*Chapter 19*) classes will prove to be useful in prevention of T2D.

The potential benefits of intervention before the onset of diabetes and aggressive treatment once the disease becomes manifest are tremendous. Identifying and treating the individual prediabetes and related CV comorbidities reduce the incidence of macrovascular disease and T2D. Early intervention in T2D certainly reduces the incidence of microvascular disease and will most likely slow the progression of the disease itself. The primary care provider is uniquely positioned to promote and provide early prevention and to have a substantial impact on lessening the burden placed on individuals and society by T2D.

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Classification

Diabetes mellitus and other categories of glucose intolerance can be divided into three main clinical categories:

- Diabetes mellitus (with four clinical subclasses)
- Gestational diabetes mellitus (GDM)
- Impaired glucose tolerance (IGT)/impaired fasting glucose (IFG).

The group of metabolic disorders that constitute diabetes result from impaired insulin action, production, or both. Features shared by these disorders are elevated plasma glucose and/or glycated hemoglobin (A1C) levels above the limits established by the American Diabetes Association (ADA) Clinical Practice Recommendations. The four clinical classes of diabetes mellitus are:

- Type 1 diabetes mellitus (insulin-dependent)
- Type 2 diabetes mellitus (non–insulin-dependent)
- GDM
- Other specific types of diabetes associated with certain conditions.

Each of these subclasses has distinctive characteristics (**Table 3.1**).

Type 1 Diabetes Mellitus and Latent Autoimmune Diabetes of Adults (LADA)

Type 1 diabetes (T1D) is defined by the presence of one or more autoantibodies that mediate the destruction of pancreatic β-cells, leading to the eventual loss of insulin production. Autoimmune markers include circulating antibodies to islet cells, endogenous insulin, glutamic acid

decarboxylase (GAD), tyrosine phosphatases IA-2 and IA-2β, or to zinc transporter 8 (ZnT8). In patients with classic acute symptoms (eg, hyperglycemia), a random plasma glucose measurement of ≥200 mg/dL is part of diagnosis, since it confirms the patient's symptoms are due to diabetes and will help direct management decisions. Patients commonly are lean at presentation and may have experienced considerable weight loss prior to diagnosis. Approximately 5% to 10% of all individuals who have been diagnosed with diabetes in the United States have T1D. Therapy with exogenous insulin is required throughout the patient's life to prevent metabolic decompensation, ketoacidosis, and death. Most patients are diagnosed with T1D before age 20, although it can develop at any age.

TABLE 3.1 — Distinguishing Characteristics of Diabetes Mellitus and Other Disorders of Glucose Intolerance

Category	Distinguishing Characteristics
Type 1 diabetes (insulin-dependent)	Any age, usually not obese, often abrupt onset, signs/symptoms usually before age 20, positive urine ketone test with hyperglycemia, insulin therapy necessary to sustain life and prevent ketoacidosis
Type 2 diabetes (non–insulin-dependent)	Usually over age 30 at diagnosis, positive family history, obese, few classic symptoms, not prone to ketoacidosis unless under severe physical stress (eg, infection), exogenous insulin usually not needed to control hyperglycemia for many years
Gestational diabetes mellitus	Occurs in women, onset or discovery of glucose intolerance during pregnancy
Latent autoimmune diabetes of adults	Age of onset <50 years, BMI <25 kg/m^2, personal or family history of autoimmune disease, insulin dependence within 6 years
Malnutrition-related diabetes mellitus	Young age (10 to 40), usually symptomatic, not prone to ketoacidosis, most require insulin therapy
Other Types of Diabetes Mellitus Associated With Certain Conditions	
Secondary to:	
Pancreatic disease	Pancreatectomy, hemochromatosis, cystic fibrosis, chronic pancreatitis
Endocrinopathies	Cushing's syndrome, acromegaly, pheochromocytoma, primary aldosteronism, glucagonoma
Drugs and chemical agents	Certain antihypertensive drugs (thiazides, diuretics, or β-blockers), glucocorticoids, estrogen-containing preparations, nicotinic acid, phenytoin, catecholamines

Associated with:	
Insulin receptor abnormalities	Acanthosis nigricans
Genetic syndromes	Lipodystrophic syndromes, muscular dystrophies, Huntington's chorea
Miscellaneous conditions	Polycystic ovary disease
Impaired glucose tolerance	Plasma glucose levels are higher after a glucose load than normal but not diagnostic of diabetes mellitus

Adapted from American Diabetes Association. *Diabetes Care*. 2022;45(suppl 1):S17–S38; Laugesen E, et al. *Diabet Med*. 2015;32(7):843-852.

LADA is roughly defined as T1D that develops later in life and has some distinguishing characteristics from classic T1D, which normally presents with DKA in childhood. LADA has a different clinical presentation that is often missed by HCPs because of the older age and absence of DKA. Beta cell destruction is much slower so DKA typically does not occur and the patient may actually respond somewhat to OADs, especially SFUs. In a relatively short period of time, the patient usually will require insulin therapy. Patients with LADA do not have some of the associated conditions and physical stigmata of T2D, in that they do not have hypertension, dyslipidemia, or central obesity. Since islet cell antibody (ICA) titers drop off after the diagnosis of T1D, use of anti-GAD antibodies is the best test to determine if a patient has LADA, since these antibodies can be detected for many years after the diagnosis.

Type 2 Diabetes Mellitus

Type 2 diabetes (T2D) is the most common type of diabetes, accounting for 90% to 95% of all diagnosed cases in the United States and is more prevalent among various non-Caucasian ethnic/racial populations, such as

American Indians, African Americans, Pacific Islanders, and Hispanics. A strong genetic basis exists for T2D (approximately 70% of patients with T2D have a positive family history of this disorder). In addition, identical-twin studies have revealed a 60% to 90% concordance for diabetes. An absence of antibodies and ketosis are two of the primary features that distinguish T2D from T1D, although it is possible to have ketonemia and acidosis with T2D.

Patients with T2D can vary considerably in their ability to secrete insulin. Insulin secretion, however, is inadequate to overcome the insulin resistance associated with this type of diabetes. Defects of insulin action (insulin resistance) are pathognomonic of T2D.

Obesity is frequently present in T2D. Approximately 90% of people with T2D are obese (20% over ideal body weight), and the chances of developing T2D double for every 20% increase in body weight in susceptible individuals. However, T2D also can develop in nonobese individuals; this is more commonly observed in older patients. The incidence of T2D increases with age and obesity in part because people tend to gain weight and especially develop visceral or central abdominal obesity.

T2D usually is diagnosed after the age of 30, although it is being diagnosed more frequently at a younger age (eg, at age 20 or below) in certain ethnic groups prone to developing diabetes. The age at onset for T2D is progressively decreasing and now develops in children and adolescents as well as in young adults. Initially, patients are often asymptomatic and only occasionally display the classic symptoms of hyperglycemia (polydipsia, polyuria, polyphagia, weight loss). Because T2D can go unrecognized for many years, the early stages of microvascular disease and frank macrovascular complications may be present by the time a diagnosis is made.

Gestational Diabetes Mellitus

Glucose intolerance that is diagnosed during the second or third trimester of pregnancy is classified as GDM. Excluded from this group are

women who had diabetes before conception. GDM occurs in approximately 4.6% to 9.2% of pregnant women and is more common in women who are older, obese, of high-risk ethnic groups, or have a family history of diabetes. This condition is important to identify because of the increased risk of fetal morbidity and mortality with GDM.

Pregnant women with risk factors for T2D should be screened by either a one-step or two-step OGTT. The one-step test employs a 75-g OGTT, with plasma glucose measurement during fasting and at 1 and 2 hours. Diagnosis of GDM is made if any of the fasting, 1-hour, or 2-hour PG values meet or exceed 95 mg/dL, 180 mg/dL, or 153 mg/dL, respectively. The two-step test first utilizes a nonfasting 1-hour 50-g glucose load test (GLT). If the PG values is ≥140 mg/dL 1 hour after the 50-g load, then it is followed by a fasting 100-g OGTT. Diagnosis of GDM is made if two or more of the fasting, 1-, 2-, or 3-hour PG levels meet or exceed 95 mg/dL, 180 mg/dL, 155 mg/dL, or 140 mg/dL, respectively. Both tests are performed between the 24th to 28th weeks of pregnancy. Women at high risk for GDM should undergo glucose testing as soon as possible. Approximately 90% to 95% of women with GDM return to normal glucose tolerance after delivery. However, women who have had GDM are at increased risk for developing T2D, with approximately 35% to 60% developing T2D within 5 to 10 years following pregnancy.

Prediabetes: Impaired Glucose Tolerance (IGT) and Impaired Fasting Glucose (IFG)

Individuals who have plasma glucose or A1C levels that are higher than normal but lower than established diagnostic values for diabetes mellitus are classified as having prediabetes (diagnostic criteria in **Table 3.2**). IFG is defined as FPG levels of 100-125 mg/dL (5.6-6.9 mmol/L) and IGT is defined as PG levels of 140-199 mg/dL (7.8-11.0 mmol/L) 2 hours after a 75-g oral glucose load. It is reasonable to consider individuals meeting these criteria, as well as those with A1C of between 5.7% and 6.4%, as those with prediabetes. This condition is common (in 2012, approximately 37% of US adults ≥20 years had prediabetes) and is considered a precursor

of T2D. Although individuals with prediabetes are more likely to eventually develop diabetes mellitus, only approximately 29% go on to develop T2D. The rate of progression is approximately 5% to 10% per year and can be influenced by:

- Ethnic origin and genetics
- Degree of obesity
- Distribution of body fat
- Sedentary lifestyle
- Aging
- Concomitant medical conditions.

TABLE 3.2 — Diagnostic Criteria for Prediabetes

	ADA Criteria	WHO/IDF Criteria
FPG	100-125 mg/dL	110-125 mg/dL
2-h PG[a]	140-199 mg/dL	140-199 mg/dL
A1C	5.7%-6.4%	n/a[b]

[a] 75-g glucose load.
[b] The WHO concluded there is insufficient evidence to make recommendations on interpreting A1C levels <6.5% (2011).

American Diabetes Association. *Diabetes Care*. 2022;45(Suppl. 1):S17–S38; Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: Report of a WHO/IDF Consultation. Geneva: World Health Organization, 2006; Use of Glycated Haemoglobin (A1C) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: World Health Organization, 2011.

Individuals with prediabetes are more susceptible to develop T2D, heart disease, and stroke. Pharmacologic therapies and nonpharmacologic interventions, such as weight reduction, improved diet, and increased physical activity through lifestyle modifications, have been shown to prevent the progression of prediabetes to T2D.

Other Specific Types of Diabetes Mellitus

This category of diabetes mellitus is the least common and includes diabetes related to certain other diseases, conditions, or drugs. Patients are placed in this category if their diabetes has a known or probable cause or is part of a specific condition or syndrome (**Table 3.2**). Hyperglycemia is present at a level that is diagnostic of diabetes. Treatment of the underlying disorder may ameliorate the diabetes; more frequently, however, it is necessary to treat the diabetes with lifestyle modification, such as diet and exercise, and medication.

Problems With Classification

Sometimes it is difficult to distinguish between T1D and T2D, especially in younger children, due to the obesity epidemic. Children with features of T2D, such as obesity, may also present with autoantibodies and ketosis. Alternatively, younger patients with T2D who are thin and taking insulin may resemble patients with T1D. In addition, some patients display the characteristics of T2D and are not susceptible to ketoacidosis, yet they are taking insulin. These patients should not be classified as T1D based solely on their insulin regimen, because they are taking insulin for glycemic control rather than as a life-sustaining therapy to prevent ketoacidosis and death.

T2D sometimes is found in children or adolescents who usually are above their ideal body weight and a member of a high-risk ethnic group susceptible to T2D. A unique type of diabetes found in the pediatric and young-adult population is called maturity-onset diabetes of the young (MODY) and is an example of an autosomal-dominant form of inheritance of diabetes. The 2008 best practice guidelines for the diagnosis of MODY include the following criteria: 1) young onset (before 25 years of age in one or more family members); 2) family history of diabetes in at least two consecutive generations; 3) lack of insulin dependence (outside the normal ‘honeymoon’ period); 4) absence of β-cell autoantibodies; 5) glycosuria at blood glucose levels below 10 mmol/L or 180 mg/dL; 6) increased sensitivity to sulfonylureas. Patients with MODY are not typically overweight, which distinguishes it from obesity-associated youth-onset

T2D. However, MODY is difficult to distinguish from T1D and T2D based on clinical characteristics alone; correct diagnosis requires genetic testing. Mutations responsible for MODY have been identified in at least 14 different genes to date; the most common is a mutation in the hepatocyte nuclear factor-1α (HNF-1α). In order to assure that these individuals receive optimal treatment, proper genetic diagnosis is important, and can be achieved through genetic testing. Each of the 6 major subtypes and 8 minor subtypes of MODY have characteristic features, largely dependent on the affected gene. For example, MODY 3 (HNF1α-MODY) is characterized by progressive childhood hyperglycemia which develops into diabetes in early adulthood; by contrast, MODY 2 (GCK-MODY) is characterized by mild and often nonprogressive hyperglycemia, and is thus typically asymptomatic. Several MODY subtypes are characterized by additional manifestations, including MODY 5 (HNF1β-MODY; renal abnormalities) and MODY 8 (CEL-MODY; exocrine abnormalities).

SUGGESTED READING

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