**TYPE 2 DIABETES MELLITUS**

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### DEFINITION

In this chapter, we discuss the pathogenesis and treatment of type 2 diabetes and other forms of the disease. See Chapter 236 for a general overview of normal carbohydrate metabolism and the complex physiology of insulin secretion and action. Although type 2 diabetes has many similarities to type 1 diabetes, there are many important differences from the vantage point of both biology and therapeutics.

Type 2 diabetes accounts for most cases of diabetes encountered in clinical practice. Patients retain some endogenous insulin secretory capacity; however, their insulin levels are low relative to their ambient glucose concentrations and magnitude of insulin resistance. Type 2 patients are not dependent on insulin for immediate survival, and ketosis rarely develops, except under conditions of great physical stress. Nevertheless, many of these patients will require insulin therapy for optimal glycemic control over time. Although type 2 diabetes has recently been found with increasing frequency in children, adolescents, and young adults, it is usually associated with advancing age; most cases are diagnosed after the age of 45 years. Type 2 diabetes has a high rate of genetic penetrance unrelated to HLA genes and is associated with obesity and a lack of physical activity. The clinical features of type 2 diabetes can be insidious; classic symptoms may be quite mild. Fatigue, weakness, dizziness, blurred vision, and other nonspecific complaints often dominate the clinical picture, but these may be tolerated for many years before the patient seeks medical attention. Moreover, if the degree of hyperglycemia is insufficient to produce any symptoms at all, the diagnosis can be made only after the development of vascular or neuropathic complications.

The general classification scheme for diabetes mellitus is summarized in Table 237-1.

### Other Specific Types of Diabetes

This category encompasses a wide variety of diabetic syndromes attributed to a specific disease, drug, or condition. Categories include genetic defects of β-cell function or insulin action, diseases of the exocrine pancreas (e.g., chronic pancreatitis), other endocrinopathies (e.g., Cushing’s syndrome, acromegaly), drug- or chemical-induced diabetes (e.g., due to glucocorticoids), infections, and other immune-mediated and genetic syndromes associated with diabetes mellitus.

Maturity-onset diabetes of the young (MODY), formerly classified as a subtype of type 2 diabetes, has now been more accurately described as a consequence of genetic research. Clinically, patients with MODY generally present in adolescence or young adulthood; unlike patients with classic type 2 diabetes, they are usually nonobese, normotensive, and normolipidemic at the time of diagnosis. MODY is a heterogeneous disorder encompassing several monogenic defects of β-cell function; it has an autosomal dominant inheritance and a penetrance exceeding 80%. Mutations of at least nine genetic loci have been identified. The most common form, MODY type 3, is associated with a mutation of HNF1α (hepatocyte nuclear factor-1α), a gene transcription factor encoded on chromosome 12. A subgroup of MODY type 2 patients has a mutation in the gene encoding glucokinase, the key enzyme responsible for the phosphorylation of glucose within the β cell and the liver. A variety of glucokinase mutations, each capable of interfering with the transduction of the glucose signal in the β cell, have been identified in different families. These forms of diabetes may respond to insulin secretagogues, such as sulfonylureas or, if needed, to insulin injections.

Severe illness (e.g., burns, trauma, sepsis) can provoke stress hyperglycemia as a result of the hypersecretion of insulin antagonistic hormones (e.g., catecholamines, cortisol). Although this may represent the unmasking of underlying diabetes, the metabolic disturbance may be self-limited and should therefore not be formally classified as diabetes until the precipitating illness has resolved (unless there is evidence of more chronic hyperglycemia, as reflected by a hemoglobin A1c [HbA1c] of 6.5% or greater). Whereas most patients can be readily classified on clinical grounds, a small subgroup of patients is difficult to categorize because they display features common to both type 1 and type 2 diabetes. Such patients are classically nonobese, with reduced insulin secretory capacity but little tendency for ketosis. Many of these patients initially respond to oral agents; however, nearly all of them will eventually require insulin therapy. Many of these patients appear to have a slowly evolving form of type 1 diabetes, with measurable titers of autoimmune markers, referred to as latent autoimmune diabetes of adulthood (LADA).

### Gestational Diabetes Mellitus

The term gestational diabetes mellitus (Chapter 236) describes women with abnormal glucose tolerance that appears or is first detected during pregnancy. Women with known diabetes before conception are not classified as having gestational diabetes. Gestational diabetes mellitus usually appears in the second or third trimester, when pregnancy-associated insulin antagonistic factors (many placentally derived) reach their peak. After delivery, glucose tolerance generally (but not always) reverts to normal. However, within 10 years, type 2 diabetes develops in most women with prior gestational diabetes; on occasion, pregnancy can precipitate type 1 diabetes as well. As a whole, gestational diabetes occurs in approximately 7% of U.S. pregnancies, accounting for approximately 200,000 cases per year; local prevalence rates may rise as high as 14% in high-risk populations. Although patients with gestational diabetes generally present with mild, asymptomatic hyperglycemia, rigorous treatment is indicated to protect against hyperglycemia-associated fetal morbidity. Most respond to diet, but pharmacotherapy is often required, with insulin remaining the standard treatment approach in these individuals.

### EPIDEMIOLOGY

Systematic screening for asymptomatic type 2 diabetes mellitus is generally limited to high-risk populations, rendering broader prevalence estimates imprecise. Total U.S. prevalence is now estimated at 8%, but probably exceeds 25% in persons older than 65 years. Type 2 diabetes is more common in Native Americans, Hispanic Americans, and African Americans, in whom the prevalence exceeds 12 to 13%, than in whites; these patients also typically present at an earlier age. Prevalence rates vary worldwide; type 2 diabetes has a propensity for Asiatic Indians, Polynesians-Micronesians, and Latin Americans. Interestingly, African blacks, Australian Aborigines, Asians, and Pacific Islanders all have an increased risk for diabetes after emigration to the United States; this may be attributable to a genetically determined inability to adapt metabolically to “Western” behavior patterns (i.e., reduced physical activity and a high-fat, high-calorie diet).

Although relatively little is known about the specific genetic abnormalities associated with type 2 diabetes, the personal factors promoting disease expression are well established. Increased age, reduced physical activity, and obesity are risk factors for the disease, especially in genetically susceptible persons. The severity and duration of obesity contribute significantly to diabetes risk; patients with high waist-to-hip ratios (i.e., central or upper body obesity) are also more prone to the disease. Family history is also important because type 2 diabetes occurs more frequently in persons with diabetic parents or siblings. Identical twin concordance rates approach 100%; in these cases, affected twins will even often develop diabetes at a similar age.

### Impaired Fasting Glucose and Impaired Glucose Tolerance

In 2008, the Centers for Disease Control and Prevention estimated that 57 million adults had prediabetes in the United States. There is only partial overlap between the impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) groups, as demonstrated by the fact that approximately 37% of patients with IFG also have IGT, whereas approximately 24% of patients with IGT also have IFG. Because of the insidious nature of both conditions, precise rates of progression to overt diabetes are difficult to establish; current estimates approach 5 to 10% per year for each condition, with even higher rates if both conditions are present. In general, IGT appears to have a greater sensitivity for predicting the future development of diabetes; it is also an independent risk factor for cardiovascular complications. Recently, high HbA1c levels (5.7 to 6.4%) have been added to the laboratory criteria that define prediabetes. As with IFG and IGT, there is imperfect concordance between individuals with HbA1c levels in this range and those with the glucose-based abnormalities that define prediabetes. Nonetheless, each identifies a group of patients at increased risk for developing diabetes and for which preventive strategies should be considered.

### PATHOBIOLOGY

Whereas the pathogenesis of hyperglycemia in patients with type 1 diabetes is reasonably straightforward (lack of insulin due to β-cell destruction), the
metabolic underpinnings of type 2 diabetes are comparatively more varied, and to a large degree enigmatic, involving defects in both insulin action and secretion. Hyperglycemia in type 2 diabetes probably results from complex genetic interactions, the expression of which is modified by environmental factors such as body weight and exercise. With type 2 diabetes, identical twin concordance rates approach 100%, although disease onset and course can vary greatly on the basis of environmental factors. Hyperglycemia itself is known to impair insulin secretion and action; elevated free fatty acid levels also play an important pathogenic role. By the time that hyperglycemia is detected, nearly all type 2 patients exhibit both defective insulin secretion and insulin sensitivity; this makes it somewhat of a challenge to determine which of the two factors is primarily responsible for the vicious cycle leading to disease (Fig. 237-1). Nonetheless, it is difficult to develop diabetes if β-cell function remains adequate for the peripheral demands for insulin action.

**TABLE 237-1**

<table>
<thead>
<tr>
<th>Fasting Plasma Glucose Level</th>
<th>2-Hour (75-g) OGGT Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg/dL</td>
<td>Normal (IGT)</td>
</tr>
<tr>
<td>100-125 mg/dL</td>
<td>IFG†</td>
</tr>
<tr>
<td>≥126 mg/dL</td>
<td>DM</td>
</tr>
</tbody>
</table>

HbA1c LEVEL

- <5.7%: Normal
- 5.7-6.4%: High risk
- ≥6.5%: DM

*These diagnostic categories are based on the combined fasting plasma glucose level and a 2-hour, 75-g oral glucose tolerance test (OGTT) result. Note that a confirmed random plasma glucose level of 200 mg/dL or higher in the appropriate clinical setting is diagnostic of diabetes and precludes the need for further testing.

DM = diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance.

**Genetics**

Although monogenic forms of diabetes have been identified (e.g., MODY types), most cases are likely to be polygenic in nature. Type 2 diabetes shows clear familial aggregation but does not segregate in classic mendelian fashion; this implies that the disease results either from a combination of genetic defects or from the simultaneous presence of multiple susceptibility genes and predisposing environmental factors. Candidate gene mutations for polygenic types of type 2 diabetes include mutations of the transcription factors like 2 (TCF7L2), the coding region of the insulin gene, peroxisome proliferator-activated receptor-γ (PPAR-γ), β-cell adenosine triphosphate-sensitive potassium channel, intestinal fatty acid–binding protein 2, calpain 10, and β3-adrenergic receptor. These and other mutations have been associated with isolated clusters of patients with type 2 diabetes. TCF7L2 has received substantial attention recently because single nucleotide polymorphisms in this gene have been strongly associated with type 2 diabetes risk and impaired insulin secretion.

**Pathogenesis**

**Insulin Secretion**

It is now quite apparent that the driving force in the progression from normal glucose tolerance to IGT to frank type 2 diabetes is the progressive loss of insulin secretory capacity. Once type 2 diabetes becomes manifested, fasting insulin levels in type 2 diabetes generally appear normal or elevated, yet they are relatively low given the degree of coexisting hyperglycemia. As the disease progresses and hyperglycemia becomes more severe, basal insulin levels eventually fail to keep up and may even decline. Indeed, autopsy studies demonstrate that β-cell mass is reduced by 50% in such patients. The insulin secretory defect usually correlates with the severity of fasting hyperglycemia and is more evident after carbohydrate ingestion. In its mildest form, the β-cell defect is subtle, involving the loss of the “first-phase” insulin response and the normal oscillatory pattern of insulin secretion. Although the overall insulin response may appear to be fairly intact, this “normal” response is actually totally inadequate to maintain glucose tolerance when it is viewed in the context of simultaneous insulin resistance. During this early stage, the β-cell defect is usually specific for glucose; other secretagogues (e.g., amino acids) maintain their potency, and insulin deficiency is thus less pronounced during the ingestion of mixed meals. Patients with more severe fasting hyperglycemia lose this capacity to respond to the other insulin secretagogues; thus, their secretory defect worsens as their disease progresses. The underlying cause of the secretory defect remains uncertain and is probably multifactorial, involving both functional and anatomic defects, and to large degree genetically determined.

Studies in rodents suggest that the loss of glucose-stimulated insulin secretion is associated with a decreased expression of GLUT 2, the primary glucose transport protein of the pancreatic β cell. Pathologic studies of islets from patients with long-standing type 2 diabetes have demonstrated amyloid-like deposits composed of islet amyloid polypeptide, or amylin, a peptide synthesized in the β cell and co-secreted with insulin. Chronic hypersecretion of amylin may lead to intra-islet precipitation of the peptide, which over time might also contribute to impaired β-cell function. Experiments in gene knockout mice suggest a potential role for impaired insulin receptor signaling in the development of impaired β-cell function. A link between insulin resistance and secretion is also suggested by the accumulation of fat within the β cell, which may interfere with normal insulin secretion. Finally, studies in patients with type 2 diabetes demonstrate reduced circulating glucagon-like peptide 1 (GLP-1) concentrations, particularly in response to meals. Whether this phenomenon is a causative factor or occurs secondarily in patients with preexisting hyperglycemia is uncertain.

**Insulin Resistance**

With few exceptions (e.g., a subgroup of African American patients), type 2 diabetes is characterized by impaired insulin action. The insulin dose-response curve for augmenting glucose uptake in peripheral tissues is shifted to the right, representing decreased insulin sensitivity, and maximal response is reduced, particularly in the setting of severe hyperglycemia. Other insulin-dependent processes, such as inhibition of hepatic glucose production and lipolysis, also show reduced sensitivity to insulin. The mechanisms responsible for insulin resistance remain poorly understood. Studies suggest that an important contributory factor is impaired mitochondrial function and the resulting accumulation of free fatty acids and their metabolites in insulin-responsive tissues (“ectopic fat theory”).

Early studies of insulin resistance focused on defects of the insulin receptor. Mutation of the insulin receptor gene can produce leprechaunism (Chapter 212), characterized by severe growth retardation, extreme insulin resistance, and early infant death. Other syndromes related to mutated insulin receptors include the Rabson-Mendenhall syndrome, also associated with tooth and nail abnormalities and pineal gland hyperplasia, and “type A insulin resistance,” most often affecting young females with acanthosis nigricans, polycystic ovaries, and hirsutism. Another example of extreme insulin resistance involves the presence of anti-insulin receptor antibodies; it is associated clinically with acanthosis nigricans and a number of autoimmune phenomena. These disorders are not involved in most patients with or at risk for type 2 diabetes.

Although insulin receptors may be abnormal in a few type 2 patients, defects in more distal “postreceptor” pathways play a far greater role in insulin resistance. One important aspect of insulin resistance is a reduced capacity for translocation of GLUT 4 to the cell surface in muscle cells. A separate defect in glycolysis synthesis also is likely to be present. Whether the defects uncovered are primary or secondary to the disturbance in glucose metabolism is not entirely known, but the bulk of the experimental data would suggest that insulin resistance is a primary defect in this disease. Potentially, a variety of genetic abnormalities in cellular transduction of the insulin signal may individually or in concert produce an identical clinical phenotype. It is uncertain whether mechanisms of insulin resistance in nonobese patients are identical to those of their obese counterparts; however, the coexistence of obesity clearly accentuates the severity of the resistant state. In particular, upper body or abdominal (compared with lower body or peripheral) obesity is associated with insulin resistance and diabetes. Intra-abdominal visceral fat
deposits, detected by computed tomography or magnetic resonance imaging, have a higher lipolytic rate than peripheral fat and are more resistant to insulin. The resulting increase in circulating free fatty acid levels promotes fat deposits within the liver and muscle, worsening insulin resistance. Intracellular free fatty acid metabolites appear to promote insulin resistance through complex mechanisms involving serine (rather than tyrosine) phosphorylation of insulin signaling molecules. Disordered cortisol secretion or enhanced local cortisol generation from relatively inactive cortisone in the adipocyte or hereditary factors may also influence the distribution of body fat, the latter contributing an additional genetic influence on the expression of disease.

Adipocyte-Derived Hormones and Cytokines
Adipocytes, once thought of as inert fat storage cells, are now known to produce a number of metabolically active hormones that may affect insulin sensitivity (Chapter 227). Leptin, for example, acts on the hypothalamus to promote satiety and energy expenditure and may accelerate glucose metabolism. Adiponectin, another fat-derived hormone, circulates at levels that correlate inversely with both adiposity and degree of insulin resistance. The administration of adiponectin to obese mice causes a transient, dose-dependent, insulin-independent decrease in circulating glucose levels; adiponectin also improves insulin sensitivity by decreasing triglycerides in the liver and muscle, probably by increasing the expression of molecules (e.g., adenosine monophosphate kinase) involved in fatty acid combustion and energy dissipation. Weight loss pharmacologically increases adiponectin, as does pharmacologic therapy that improves insulin sensitivity. Interestingly, adiponectin may have some beneficial effects on atherosclerosis, which may explain at least to some degree the increased prevalence of cardiovascular disease in obesity and type 2 diabetes. Finally, adipose tissue is an abundant source of the cytokine tumor necrosis factor-α, which is known to inhibit muscle glucose metabolism by inducing serine phosphorylation of insulin-signaling molecules. The precise impact that these and other adipocyte-derived factors (resistin, angiotensinogen, interleukin-6, transforming growth factor-β, and plasminogen activator inhibitor 1) exert on insulin resistance and on diabetes and its vascular complications is an active area of scientific research but has yet to be firmly established.

Glucotoxicity and Lipotoxicity
Hyperglycemia per se impairs the β-cell response to glucose and promotes insulin resistance. Reversal of this “glucotoxicity” can disrupt the vicious circle that perpetuates hyperglycemia (see Fig. 237-1). Similarly, circulating lipids can also adversely affect glucose metabolism through complex mechanisms involving serine (rather than tyrosine) phosphorylation of insulin signaling molecules. Disordered cortisol secretion or enhanced local cortisol generation from relatively inactive cortisone in the adipocyte or hereditary factors may also influence the distribution of body fat, the latter contributing an additional genetic influence on the expression of disease.

What Is the Primary Defect?
It remains uncertain whether insulin resistance or defective insulin secretion is the primary defect in type 2 diabetes (Fig. 237-2). This issue is difficult to resolve once diabetes has developed; therefore, research attention has focused primarily on high-risk nondiabetic subjects. Studies in high-risk populations (e.g., Pima Indians, Mexican Americans) have suggested that insulin resistance is the initial defect; similar findings have been reported in first-degree relatives of type 2 diabetic patients and in healthy prediabetic offspring of two diabetic parents. Interestingly, hyperinsulinemia has been detected in prediabetic subjects as early as one to two decades before clinical onset, suggesting that the development of diabetes can be exceedingly slow. Although these studies support the view that insulin resistance generally antedates insulin deficiency, the presence of insulin resistance alone is generally insufficient to generate hyperglycemia; this implies that for diabetes to occur, impaired insulin secretion is required (see Fig. 237-2). It is possible that the appearance of a secretory defect is a secondary phenomenon resulting from “β-cell exhaustion,” excess fatty acid delivery, amylin accumulation, or factors associated with β-cell growth. Perhaps more likely, diminished insulin secretion may result from an independent defect that becomes evident only on chronic β-cell stimulation, such as a subtle genetic defect in insulin signaling or β-cell replication.

The sequence of events described—underlying insulin resistance followed by a secretory defect—is common but clearly does not describe all type 2 diabetic patients. For example, a subgroup of African American patients exhibits little or no insulin resistance. (An insulin deficiency–predominant phenotype is also encountered infrequently in clinical practice in other racial groups, although, admittedly, many of these individuals may potentially have a slowly progressive form of type 1 diabetes.) In addition, diminished glucose-stimulated insulin secretion is seen in women with gestational diabetes in whom type 2 diabetes later develops. Finally, the demonstration of functional β-cell-associated gene mutations in patients with MODY indicates that primary β-cell defects are capable of producing a similar phenotype. Taken together, these lines of evidence strongly suggest that type 2 diabetes cannot be explained by insulin resistance alone or indeed by any single pathogenic mechanism.

**DIAGNOSIS**
The diagnosis of diabetes mellitus is straightforward when classic symptoms of polyuria, polydipsia, and unexplained weight loss are present. In these cases, a random (or “casual”) plasma glucose measurement of 200 mg/dL or more is sufficient to confirm the diagnosis. Although glycosuria is strongly suggestive of diabetes, urine test results should never be used exclusively to diagnose diabetes because an altered renal threshold for glucose excretion can produce similar findings. If suspected diabetes is not confirmed through random glucose determination, additional diagnostic testing should be performed.

An 8-hour (overnight) fasting plasma glucose measurement is most convenient; diabetes is established if fasting glucose levels are 126 mg/dL or higher on two separate occasions. Alternatively, a 75-g oral glucose tolerance test may be employed. The oral glucose tolerance test should be performed after an overnight fast, with use of a glucose load containing 75 g of anhydrous glucose dissolved in water; 2-hour postload glucose levels of 200 mg/dL or higher confirm the presence of diabetes. An important note about the oral glucose tolerance test: although it is able to detect diabetes in its earliest stage, this test should be performed under controlled conditions to ensure its accuracy. Common factors that can nonspecifically interfere with the oral glucose tolerance test result include antecedent dietary carbohydrate restriction, bedrest or severe inactivity, medical or surgical stress, drugs (e.g., thiazides, β-blockers, glargicorticois, phenytoin), smoking, and anxiety from repeated phlebotomies. As a result, the oral glucose tolerance test should not be performed in acutely ill patients, and patients undergoing the oral glucose tolerance test should ideally stop smoking and consume a liberal carbohydrate diet for at least 3 days before testing. More recently, with global standardization of HbA1c assays, this test is now widely endorsed as an acceptable, and more convenient, screening test for diabetes, with the diagnostic cutoff point set at 6.5%. This threshold was chosen because it correlates with the presence of retinopathy, similar to the diagnostic thresholds for fasting and 2-hour plasma glucose.

The current (2010) American Diabetes Association (ADA) criteria (see Table 237-1) for the diagnosis of diabetes mellitus are as follows. In the absence of unequivocal hyperglycemia with acute metabolic decompensation, each criterion should be confirmed by repeated testing on a separate occasion:

1. Classic symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) plus random plasma glucose concentration ≥ 200 mg/dL (≥11.1 mmol/L); or

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**FIGURE 237-2.** A proposed sequence of events leading to the development of type 2 diabetes. Insulin resistance resulting from genetic influences, central obesity, inactivity, or a combination of these factors leads over time to a progressive loss of the β-cell’s capacity to compensate for this defect.
2. Fasting (28-hour) plasma glucose concentration ≥126 mg/dL (≥7.0 mmol/L), or
3. A 2-hour postload plasma glucose concentration ≥200 mg/dL (≥11.1 mmol/L) during a 75-g oral glucose tolerance test; or
4. An HbA1c ≥6.5% (nonfasting).

In certain scenarios, clinicians may have available to them results from easily obtained tests, namely, fasting plasma glucose and HbA1c. Not uncommonly, the results of these tests may be discordant. That is, a patient may have an HbA1c of 6.5% or greater but a “subdiabetic” fasting plasma glucose, or vice versa. In this circumstance, it is recommended that the diagnosis default to the most abnormal test because both measures correlate with retinopathy risk.

The two traditional risk categories for diabetes, IFG and IGT, are associated with an increased risk for development of diabetes mellitus as well as subsequent cardiovascular events, with IGT being a much stronger predictor for both sequelae. Diabetes mellitus is established if fasting glucose levels are 126 mg/dL or higher; however, a fasting glucose concentration of 99 mg/dL is now designated the upper limit of normal. Patients with fasting glucose levels between 100 and 125 mg/dL are classified as having IFG (see Table 237-1). Because individuals with IFG may exhibit significant postprandial hyperglycemia, a 75-g oral glucose tolerance test, a diagnostic test. During the 75-g oral glucose tolerance test, 2-hour postload glucose concentrations of 200 mg/dL or higher are diagnostic of diabetes; patients with levels between 140 and 199 mg/dL are defined as having IGT. Patients displaying IFG and IGT simultaneously have a greater risk for development of diabetes mellitus. It should be noted that the thresholds that define these “states” are somewhat arbitrary because the risk for diabetes actually runs along a continuum. In fact, the World Health Organization, which is in accord with the other diagnostic thresholds, has kept the lower bound of the IFG range at 110 mg/dL because individuals with levels above this range appear to be at increased cardiovascular risk, similar to those with IGT. As noted previously, the ADA has also recently endorsed the use of the HbA1c for diabetes screening, based on the recommendations of the International Expert Committee, with a diagnostic threshold of 6.5% or higher. In so doing, it considered elevated but not frankly diabetic levels to represent high risk, defining this range as 5.7 to 6.4%. Table 237-1 summarizes the diagnosis of IFG, IGT, and overt diabetes mellitus. Patients with IFG or IGT or increased glycohemoglobin, each of which may be referred to as prediabetes, should be advised about healthy lifestyle changes, including diet and exercise, and should be screened annually for progression to diabetes. In very high-risk individuals, such as those with both IFG and IGT, a Consensus Statement from the ADA and the European Association for the Study of Diabetes (EASD) has proposed that, in addition to lifestyle changes, metformin be considered as adjunctive therapy (see Prevention).

The clinical utility and cost-effectiveness of screening for diabetes mellitus have never been directly demonstrated. However, because patients with diabetes may harbor the disease for many years before symptoms are appreciated, the ADA has endorsed the screening at 3-year intervals beginning at 45 years of age (Table 237-2). More frequent screening is advised for high-risk individuals, such as those with a personal history of IFG, IGT, gestational diabetes mellitus, obesity, hypertension, or dyslipidemia, patients in high-risk ethnic groups, and patients with first-degree relatives with diabetes. In most cases, a fasting plasma glucose level has been the screening test of choice; however, the oral glucose tolerance test has the advantage of detecting patients with IGT and early diabetes. The more convenient HbA1c test will likely be used more often now that it is endorsed as a screening test by the ADA, but there is little information about its predictive value across various groups of patients.

**Gestational Diabetes Mellitus**

Because even mild glucose elevations can have serious adverse effects on a developing fetus, an aggressive screening approach is recommended during pregnancy (Chapter 247). Women with a high clinical risk of gestational diabetes (personal history of gestational diabetes mellitus, obesity, glycosuria, or a strong family history of diabetes) should undergo screening as soon as possible after conception; in these patients, screening before pregnancy is preferred if possible. At 24 to 28 weeks of gestation, screening is recommended for all pregnant women, except those in the lowest risk category who meet all of the following clinical characteristics:

**TABLE 237-2 CRITERIA FOR DIABETES SCREENING IN ASYMPTOMATIC INDIVIDUALS**

| Criterion                                                                                      |
|                                                                                               |
| 1. Testing should be considered in all adults who are overweight (BMI > 25 kg/m²) and have additional risk factors:                     |
| • Physical inactivity                                                                         |
| • A first-degree relative with diabetes                                                       |
| • High-risk ethnic population (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)           |
| • Delivered a baby weighing more than 9 pounds or diagnosed with gestational diabetes mellitus|
| • Systemic hypertension (blood pressure > 140/90 mm Hg or on antihypertensive therapy)       |
| • High-density lipoprotein cholesterol level < 35 mg/dL or triglyceride level > 250 mg/dL     |
| • Polycystic ovary syndrome                                                                     |
| • Hemoglobin A1c ≥ 5.7%, impaired glucose tolerance or impaired fasting glucose on prior testing |
| • Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)                           |
| • History of cardiovascular disease                                                            |

In pregnant women, a casual plasma glucose level of 200 mg/dL or higher or a confirmed fasting plasma glucose level of 126 mg/dL or higher establishes the diagnosis of gestational diabetes mellitus and precludes the need for a glucose challenge. In the absence of overt hyperglycemia, a screening 1-hour 50-g glucose challenge test should be performed between 24 and 28 weeks of gestation. If the fasting glucose level is 105 mg/dL or higher or the 1-hour postload value is 140 mg/dL or higher, a diagnostic 3-hour 100-g oral glucose tolerance test is indicated. Gestational diabetes is then diagnosed if two or more values equal or exceed the upper limits of normal: fasting, 95 mg/dL; 1 hour, 180 mg/dL; 2 hour, 155 mg/dL; and 3 hour, 140 mg/dL. To save time and effort, proceeding directly to the 100-g diagnostic oral glucose tolerance test is an acceptable alternative, particularly in those deemed at higher risk. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study included more than 25,000 pregnancies, examining adverse clinical outcomes associated with mild elevations in plasma glucose during oral glucose tolerance testing. The investigators found that increases in plasma glucose above 75 mg/dL fasting, 105 mg/dL at 1 hour, and 90 mg/dL at 2 hours were associated with a higher risk for several adverse fetal and maternal outcomes (e.g., increased birthweight, primary cesarean delivery, and neonatal hypoglycemia). Importantly, no specific glucose thresholds could be identified, suggesting that adverse outcomes occur over a continuum of blood glucose elevations during pregnancy. These data will likely lead to a reevaluation of the current screening guidelines and diagnostic categories for gestational diabetes.

**Complications**

As discussed in Chapter 236, the Diabetes Control and Complications Trial (DCCT), involving solely patients with type 1 diabetes, conclusively determined that improved glucose control reduces the risk for microvascular complications. It was assumed but not entirely known if the same relationship would apply to patients with type 2 diabetes. Ultimate evidence for such a benefit came from the United Kingdom Prospective Diabetes Study (UKPDS). The UKPDS initially recruited 5102 patients with newly diagnosed type 2 diabetes; after 3 months of diet therapy, the 3867 patients with fasting glucose ≤110 mg/dL were randomized into the treatment arms.
glucose levels between 6.1 and 15.0 mmol/L (110 and 270 mg/dL) were randomized to a more intensive regimen, consisting of sulfonylurea or insulin, or maintained on the conventional dietary regimen, focused primarily on symptom reduction. Subjects were monitored for an average of 10 years. Although glyemic control gradually deteriorated in all groups, the intensified treatment group had lower overall mean HbA1c levels than their conventionally treated counterparts (7.0% vs. 7.9%). This modest improvement was associated with 25% and 12% reductions in all microvascular complications (P < 0.001) and any diabetes-related event (P = 0.03), respectively. The intensified treatment group also experienced a 16% reduction in a combined end point of nonfatal or fatal myocardial infarction or sudden death—that did not quite reach statistical significance (P = 0.052). Epidemiologically, a continuous relation between HbA1c values and all-cause mortality was demonstrated by the UKPDS study. The modest improvement in glyemic control associated with the intensified regimen was observed in a smaller substudy within the UKPDS, 753 overweight patients were randomized to metformin versus diet. Metformin-treated subjects experienced relative risk reductions of 32% for any diabetes-related end point (P = 0.02), 39% for myocardial infarction (P = 0.01), 43% for diabetes-related death (P = 0.02), and 36% for all-cause mortality (P < 0.01). Moreover, among patients allocated to intensive control, metformin had a greater effect than sulfonylurea or insulin on any diabetes-related end point, stroke, and overall mortality. These data suggested a cardiovascular benefit to metformin in overweight diabetic patients compared with either sulfonylureas or insulin.

In the more recent 10-year follow-up study of 3277 patients from the original UKPDS cohort, clinical outcomes were assessed using the original treatment assignment. Differences in HbA1c were lost between groups after the first year of follow-up, as occurred in the DCT long-term follow-up study. Despite this, however, relative risk reductions for any diabetes-related end point (P = 0.04) and microvascular disease events (24%, P = 0.001) were consistent with those observed in the sulfonylurea-insulin cohort. In addition, as more events occurred over time, significant relative risk reductions for myocardial infarction (15%, P = 0.001) and all-cause mortality (13%, P = 0.007) emerged. In the metformin- assigned subjects, risk reductions of 21% (P = 0.01) were maintained throughout the follow-up period for any diabetes-related event; 33% (P = 0.005) for myocardial infarction, and 27% (P = 0.002) for all-cause mortality. By comparison, more aggressive treatment to lower HbA1c below 6.0% in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial increased 5-year mortality despite reducing the risk of nonfatal myocardial infarction.

What conclusions can be drawn from these various studies? The primary message is that “glucose matters”—particularly the treatment strategies that have been used in the course of the disease and especially for microvascular complications. In both type 1 and type 2 diabetes patients who are willing and able to participate actively in their management, the goal should be to achieve the best possible level of glyemic control as rapidly as possible without undue risk. These studies also demonstrate that most patients benefit from lower glucose levels, even if normalization is not achieved. For most type 2 patients, effective glucose reductions can be achieved by diet, oral agents, or less complicated insulin regimens than are required in type 1 diabetes. Although a statistically significant benefit on macrovascular outcomes could not be detected in the sulfonylurea-insulin tight control arm of the UKPDS, this may have been limited by the HbA1c convergence during the follow-up period in the intensified groups. Metformin had a more convincing beneficial effect in this regard. It is also noteworthy that extensive epidemiologic data have shown a linear relationship between glycemia and cardiovascular events—even into the “normal” range for glucose. Accordingly, it was theorized by some that in order to achieve substantive cardiovascular risk reduction by glycemic control, euglycemia needed to be achieved. This was the hypothesis tested by an important trio of clinical cardiovascular trials recently reported in patients with type 2 diabetes (see later). Finally, a central conclusion from the UKPDS was that β-cell function continues to decline after the diagnosis of diabetes is made, mandating more aggressive treatment regimens.

### Glycemic Control and Cardiovascular Disease Outcomes

Although there is a strong and irrefutable epidemiologic association between glycemic control and cardiovascular events and mortality, clinical trial data to support an effect of glucose control to reduce macrovascular events has been generally elusive. Some had proposed that this phenomenon might reflect a failure of earlier trials to normalize glycemia, which might actually have required the influence of the action of insulin once it was initiated. As a result, several large randomized clinical trials (ACCORD 4 Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], 5 and the Veterans Affairs Diabetes Trial [VADT] 6 were initiated in an attempt to answer this question. Each trial examined the potential cardiovascular benefit of more intensive glucose control (HbA1c, target, 6 to 6.5%) compared with standard therapy over a period of 3 to 5 years in patients with long-standing type 2 diabetes, most of whom had evidence of cardiovascular disease (CVD) (Table 237-3). In each circumstance, the study failed to reduce CVD outcomes. In ADVANCE, the primary end point, a composite of both microvascular and macrovascular events, was modestly reduced in the intensive control arm, but this was driven solely by a reduction in renal outcomes. On the other hand, in ACCORD, all-cause mortality was actually increased by 22% in the intensive therapy cohort, mainly driven by increased cardiovascular mortality. The explanation for this finding remains controversial, however. Hypoglycemia was definitely more common in patients who died in both intensive and standard control groups, but subsequent analyses have not been able to demonstrate a precise cause-and-effect relationship. Whether the results may have reflected significant weight gain or the use of complex polypharmaceutical regimens (most participants in ACCORD’s intensive arm were receiving at least three oral agents simultaneously with or without aggressive insulin strategies) is also not known. Importantly, the results of ACCORD, ADVANCE, and VADT do not invalidate the earlier findings from the DCCT and UKPDS. Those studies were quite different insofar as they enrolled different types of patients—those with type 1 diabetes in the DCCT and newly diagnosed type 2 patients without underlying CVD in the UKPDS. Additionally, the patients in the UKPDS were randomized to “intensive control” strategies that were not nearly as stringent as those pursued in the more recent trials, and in the DCCT, the comparator “conventional control” group essentially had poorly controlled type 1 diabetes. So, a rational synthesis of the data would appear to be that the target of lowering HbA1c to approximately 7% will result in major reductions in microvascular disease risk and, over time, a modest benefit on cardiovascular end points in patients in the early stages of the disease without preexisting cardiovascular complications. However, more intensive control in an attempt to near-normalize glucose levels, especially if applied to older patients with significant risk for or preestablished cardiovascular disease, leads to no further benefit and to apparent adverse effect 7 over a treatment duration of 3 to 5 years. Given that these trials examined patients at a later stage of diabetes, they cannot answer the question of whether near-normalization of blood glucose control may have a cardiovascular benefit when initiated at the time of diagnosis and maintained for a longer duration, before vascular complications can become established.

### Table 237-3 Major Clinical Trials to Test the Association Between Glycemic Control and Cardiovascular Disease Outcomes

<table>
<thead>
<tr>
<th>STUDY PARAMETER</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>10,251</td>
<td>11,140</td>
<td>1791</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>66</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>32</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Mean follow-up (yr)</td>
<td>3.5</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Hemoglobin A₁c targets</td>
<td>&lt;6.0% vs. 7.0-7.9%</td>
<td>≤65% vs. standard</td>
<td>≤6% vs. 8.9%</td>
</tr>
<tr>
<td>Mean baseline HbA₁c</td>
<td>8.3%</td>
<td>7.5%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Mean endpoint HbA₁c</td>
<td>INT: 6.4% vs. STD: 7.5%</td>
<td>INT: 6.3% vs. STD: 7.0%</td>
<td>INT: 6.9% vs. STD: 8.4%</td>
</tr>
<tr>
<td>Major macro- or microvascular event</td>
<td>0.9 (0.82-0.98), P = .01</td>
<td>0.88 (0.74-1.05), P = .14</td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction/stroke, cardiovascular death</td>
<td>HR 0.9 (0.78-1.04), P = .16</td>
<td>0.94 (0.84-1.06), P = .32</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>HR 1.22 (1.01-1.46), P = .04</td>
<td>HR 0.93 (0.83-1.06), P = .28</td>
<td>1.07 (0.81-1.42), P = .62</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>HR 0.76 (0.62-0.92), P = .004</td>
<td>0.96 (0.77-1.22), P = .82 (0.59-1.14), P = .24</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemic events</td>
<td>INT: 10.5% vs. STD: 3.5%, P &lt; .001</td>
<td>INT: 2.7% vs. STD: 1.5%, P &lt; .001</td>
<td>INT: 8.5% vs. STD: 3.1%, P = .000</td>
</tr>
<tr>
<td>Weight change</td>
<td>&gt;10 kg, INT: 27.8% vs. STD: 14.1%, P &lt; .001</td>
<td>INT: −1.1 kg vs. STD: 4.1%, P &lt; .001</td>
<td>INT: +1.8% vs. STD: 4.1%, P = .01</td>
</tr>
</tbody>
</table>

HR = hazard ratio; INT = intensive control group; NS = not significant; STD = standard control group.

General Measures

As in individuals with type 1 diabetes, the primary long-term goals in type 2 patients are to minimize complications and to preserve the patient’s sense of clinical well-being. Glucose control should not be addressed in a vacuum. Lifestyle modification should be the primary focus of the patient’s care. Accordingly, aggressive lowering of lipids and blood pressure should be routinely incorporated into the treatment program.

In many type 2 diabetes patients, diet and exercise are the only therapeutic interventions required to restore metabolic control. As a result, drug therapy is not required in all patients and may be avoided in motivated individuals who have embraced the important concepts of a healthy lifestyle and can achieve their glycemic targets nonpharmacologically. However, it should also be realized that type 2 diabetes tends to be less responsive, and the use of antihyperglycemic medications is usually a wise maneuver. Indeed, a consensus statement, sponsored by the ADA and EASD on the treatment of hyperglycemia in type 2 diabetes, has advised using metformin (barring any contraindications) along with lifestyle change at diagnosis.

Diet

Irrespective of initial weight, modest weight reduction (on the order of 5 kg) in obese diabetic patients leads to improved glycemic control. The dramatic impact of weight loss is mediated by changes in insulin-responsive tissues as well as by enhanced β-cell activity; insulin resistance diminishes, glucose production decreases, and insulin secretion is improved. The beneficial effects of weight loss are not restricted to glucose; dietary therapy also yields improved lipoprotein profiles and systemic blood pressure. In general, it matters little how weight loss is achieved, provided good health is preserved and adequate nutrition is maintained. Successful weight loss (Chapter 227) is best achieved by the combination of a supportive environment that enables the patient to achieve the gradual attainment of specific goals, and a weight-loss strategy that facilitates increase in energy expenditure, and long-term behavior modification. Please see Table 236-3 in Chapter 236 for lifestyle changes advised for patients with diabetes.

In sedentary diabetic patients, maintenance calorie requirements can be as low as 20–25 kcal/kg/day. In these individuals, depending on baseline weight, the classically prescribed 1800-kcal diet is often inadequate in producing weight loss. It is sensible to begin with a nutritionally sound, individually tailored diet that is aimed at producing a calorie deficit of approximately 500 kcal/day. Because a calorie deficit of about 3500 kcal is required to lose 1 pound of body fat, weight loss by this method can be expected at 1 pound per week. Although this might sound too gradual for the individual eager to lose weight quickly, progressive success at this rate (which is admittedly, very difficult) will result in substantial weight loss after 1 year. For obese patients with a history of multiple failed weight loss attempts, very low calorie diets (<1000 kcal/day) can be useful when they are carried out under medical supervision. Orlistat, a gastrointestinal lipase inhibitor that reduces dietary fat absorption, can be a moderately effective adjunct for achieving weight loss in some patients; it may also improve glycemic control and lipoprotein profiles. It is associated, however, with unpleasant side effects. Sibutramine is another marketed weight loss agent, but it, too, has limited efficacy, may increase blood pressure, and in a large long-term clinical trial was associated with a cardiovascular excess. Most patients are unable to maintain low-calorie diets for an extended period. If they are successful, most patients will resume higher-calorie diets and regain lost weight. In patients with type 2 diabetes, metabolic factors may also contribute to difficulty maintaining weight loss. Dieting reduces glycemia and therefore lessens urinary glucose loss. Also, the expected decrease in basal metabolic rate during weight loss is accentuated in diabetic patients because weight loss reverses both accelerated gluconeogenesis and the futile cycling of substrates; these conditions, commonly seen in poorly controlled diabetes, decrease use of excess energy that has been ingested in the hyperglycemic state.

A popular alternative to diet is bariatric surgery; both Roux-en-Y gastric bypass and gastric banding procedures are being performed with increased frequency in both obese patients with and without diabetes. Without question, these techniques result in greater degrees of weight loss than are usually achieved through diet or medications. Both short-term and long-term safety considerations persist, although several longitudinal studies have suggested an overall health benefit. Importantly, in patients with type 2 diabetes, very low glycemic levels normalize postoperatively, and antihyperglycemic therapy can be stopped or at least markedly curtailed. The rapidity of the improvement in glucose levels, which occurs before substantial weight loss has occurred, suggests a direct metabolic benefit, perhaps owing to rapid onset of severe calorie deprivation or altered transit of nutrients through the bowel, or both, which might be promoting the actions of incretins on glucose metabolism. Even when diabetic patients cannot lose weight, a careful meal plan is a valuable tool for reducing their risk for cardiovascular disease. This benefit is best achieved by restricting saturated fats and cholesterol and by raising the dietary content of carbohydrates and monounsaturated fats. It is now appreciated that a diet that is relatively high in carbohydrate (>45% to 50%) may improve insulin action and glycemic control, particularly in patients with mild hyperglycemia. In patients with more severe fasting hyperglycemia or with triglyceride elevations aggravated by high-carbohydrate diets, reduced carbohydrate intake (<45% of total calories) and greater reliance on monounsaturated fats may be preferable. It has also been assumed that carbohydrate intake should be focused on complex carbohydrates (starches) and that sucrose should be avoided; however, evidence supporting these assumptions is scarce. Simple sugars raise glucose levels to an extent similar to that with complex carbohydrates; thus, total carbohydrate intake, rather than type of carbohydrate, should be the primary consideration. Fiber-containing carbohydrates such as oats, legumes, and fruit peptic may also be beneficial because fiber blunts meal-induced glucose excursions by delaying gastric emptying and carbohydrate absorption. Fiber helps prevent constipation and may also contribute to lowering of triglyceride and low-density lipoprotein (LDL) cholesterol.

Diabetic patients with normal lipid profiles are encouraged to follow the recommendations of the National Cholesterol Education Program (NCEP) by limiting total fat intake to less than 30% of total calories, with less than 10% of calories as saturated fat and less than 300 mg/day of dietary cholesterol (see Table 237-3). If LDL levels are elevated, stricter recommendations apply (NCEP Step II diet), with less than 7% of calories as saturated fat and less than 200 mg/day of dietary cholesterol. Despite a lack of supporting scientific evidence, moderation of dietary protein is also currently recommended for patients with diabetes; this issue assumes much greater importance in patients with proteinuria and overt diabetic nephropathy.

Exercise

Regular exercise is a powerful (and often forgotten) adjunct in the treatment of type 2 diabetes. Long-term studies demonstrate consistent beneficial effects of regular exercise on metabolic control and insulin sensitivity that can be maintained for several years. Exercise also facilitates weight loss and its maintenance, which further improves glycemic control and also has beneficial effects on cardiovascular risk and general well-being. Regular exercise lowers triglyceride-rich very low density lipoprotein (VLDL) levels, raises high-density lipoprotein (HDL) levels, and improves fibrinolytic activity. In general, moderate levels of exercise should be prescribed most days of the week (see Table 236-3 in Chapter 236). Limitations may be imposed by preexisting coronary or peripheral vascular disease, proliferative retinopathy, peripheral or autonomic neuropathy, and poor glycometric control.

Medical Therapy

Oral Glucose-Lowering Agents

Sulfonylureas were the oral agents available in the United States for more than four decades. Over the decade and a half since the 1995 approval of metformin by the U.S. Food and Drug Administration (FDA), many new classes of oral agents have become available for the treatment of type 2 diabetes (Table 237-4 and Fig. 237-3). Indeed, at present there are as many classes to treat glucose in type 2 diabetes as there are antihypertensive medication categories. Currently available noninsulin classes include the sulfonylureas, nonsulfonylurea insulin secretagogues (glinides), biguanides, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide (GLP)-1 agonists, amylin mimetics, dipeptidyl peptidase (DPP)-4 inhibitors, bile acid sequestrants, and dopamine-2 agonists. Oral agents are indicated in patients in whom diet and exercise fail to achieve treatment goals and may be favored over insulin in older patients with relative mild degrees of hyperglycemia. Patients with more severe hyperglycemia may require insulin during the initial phases of treatment; once glucose levels have stabilized and the “toxic” effects of severe hyperglycemia on β-cell function and insulin action have been minimized, many of these patients may then be converted to oral agents. Of these agents, rosiglitazone must be used cautiously because of its increased risk of heart failure and myocardial infarction compared with other agents.

For a detailed review of the oral antihyperglycemic agents, refer to the online version of this chapter. Table 237-4 summarizes the key aspects of each drug class.

Sulfonylureas

Sulfonylureas are insulin “secretagogues” that act through specific receptors on the β-cell membrane. Drug-receptor binding acts to close adenosine triphosphate–dependent potassium channels, resulting in cellular depolarization, calcium influx, and translocation of insulin secretory granules to the β-cell surface. The resulting release of insulin into the portal vein rapidly suppresses hepatic glucose production and later facilitates peripheral glucose utilization. Insulin resistance may diminish as well, but as a secondary consequence of the reversal of glucotoxicity. Because sulfonylureas rely on a preserved β-cell response, they are ineffective in the treatment of type 1 diabetes. They are also ineffective in type 2 diabetic patients with markedly impaired β-cell function.

Although the sulfonylureas differ in relative potency, effective dosage, metabolism, and duration of action, these differences have marginal significance from a clinical standpoint (see Table 237-3). Each drug has similar hypoglycemic effects; at maximally effective doses, an average drop in HbA1c of 1 to 2% is expected, correlating to average fasting plasma glucose reductions of 40 to 80 mg/dL. Drugs that are heptatically metabolized and have a shorter
duration of action have advantages in elderly patients with impaired renal function (who are more vulnerable to hypoglycemia) but may be less effective in practice because of noncompliance with multiple dosing schedules. Conversely, longer-acting agents can be dosed once daily, enhancing compliance but increasing the risk for prolonged hypoglycemia. After the appropriate drug is chosen, treatment is initiated at low doses, with dose increases every 1 to 2 weeks until either treatment goals are met or “maximally effective” doses are reached. Note that for all sulfonylureas, efficacy plateaus at about 50% of the listed maximal dose; above these maximally effective doses, little clinical benefit is derived from dose escalation, and additional therapies should be considered.

Most patients with type 2 diabetes initially respond to sulfonylureas with improved glycemic control. However, 10 to 20% of patients show little or no response and are referred to as primary drug failures. Many other patients experience the loss of drug effect after years of successful therapy; these secondary drug failures occur at rates of 5 to 10% per year mainly because of progressive β-cell failure, which is a well-recognized feature of the underlying disease process. Whether sulfonylurea drugs tax the β-cell and hasten its demise (β-cell exhaustion) is a point of controversy. Recent studies do suggest that this class of agents, although very effective, has less durability than agents that focus on the body's response to insulin, such as metformin or thiazolidinediones.

In clinical practice, early signs of secondary drug failure should provoke renewed attempts to reinforce diet and exercise as well as a reassessment of drug dosage. The reappearance of hyperglycemia despite maximally effective

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**TABLE 237-4 ORAL AGENTS AVAILABLE FOR TREATMENT OF DIABETES MELLITUS**

<table>
<thead>
<tr>
<th>AGENT</th>
<th>EXAMPLES</th>
<th>MECHANISM</th>
<th>ACTION</th>
<th>↓ IN HEMOGLOBIN A1C (%)</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>First generation: Chlorpropamide; Tolbutamide</td>
<td>Closes K_ATP channels</td>
<td>↑ Pancreatic insulin secretion</td>
<td>1-2%</td>
<td>↓ Microvascular risk</td>
<td>Hypoglycemia</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td>Second generation: Glipizide; Glimepiride</td>
<td></td>
<td></td>
<td></td>
<td>Convenience</td>
<td>Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May blunt myocardial ischemic preconditioning</td>
<td>? β-cell “exhaustion”</td>
<td></td>
</tr>
<tr>
<td>Glinides</td>
<td>Repaglinide; Nateglinide</td>
<td>Closes K_ATP channels</td>
<td>↑ Pancreatic insulin secretion</td>
<td>1-1.5%</td>
<td>More physiologic</td>
<td>Hypoglycemia, weight gain,</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ Postprandial glucose</td>
<td>May blunt myocardial ischemic preconditioning</td>
<td>? β-cell “exhaustion”</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dosing frequency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>Metformin</td>
<td>Activates AMPK</td>
<td>↓ Hepatic glucose production</td>
<td>1-2%</td>
<td>Weight loss/weight neutrality</td>
<td>Diarrhea, abdominal cramping</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No hypoglycemia</td>
<td>Lactic acidosis risk (rare)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dosing frequency</td>
<td>Vitamin B12 deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple contraindications</td>
<td>to consider (e.g., CKD)</td>
<td></td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Rosiglitazone; Pioglitazone</td>
<td>Activates PPAR-γ</td>
<td>↑ Peripheral insulin sensitivity</td>
<td>0.5-1.5%</td>
<td>No hypoglycemia</td>
<td>Weight gain</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ β-cell preservation</td>
<td>Edema/heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Triglycerides</td>
<td>Bone fractures (women)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ HDL-C</td>
<td>DLDL-C</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ CVD</td>
<td>(pioglitazone)</td>
<td></td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
<td>Acarbose; Miglitol</td>
<td>Blocks SB α-glucosidase</td>
<td>↓ Intestinal carbohydrate absorption</td>
<td>0.5-1%</td>
<td>↑ ↑ CVD</td>
<td>Gas, abdominal bloating</td>
<td>$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsystemic medication</td>
<td>Dosing frequency</td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Exenatide; Lisinagliptide</td>
<td>Activates GLP-1 receptors</td>
<td>↑ Insulin secretion ↓ Glucagon secretion Slos gastric emptying ↑ Satiety</td>
<td>1%</td>
<td>↑ ↑ CVD</td>
<td>Nausea/vomiting</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ β-cell preservation</td>
<td>? Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Cardiovascular benefits</td>
<td>? C-cell hyperplasia/tumors</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Injectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylin mimetics</td>
<td>Pramlintide</td>
<td>Activates amylin receptors</td>
<td>↑ Glucagon secretion Slos gastric emptying ↑ Satiety</td>
<td>0.5%</td>
<td>Weight loss</td>
<td>Nausea/vomiting</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ Postprandial glucose</td>
<td>Dosing frequency</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Sitagliptin; Saxagliptin</td>
<td>Inhibits DPP-4, ↑ endogenous incretins</td>
<td>↑ Insulin secretion ↓ Glucagon secretion</td>
<td>0.5-0.8%</td>
<td>No hypoglycemia</td>
<td>↑ Urticaria/angioedema</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>? Pancreatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile acid sequestrants</td>
<td>Colesevelam</td>
<td>Binds bile acid cholesterol</td>
<td>Unknown</td>
<td>0.5%</td>
<td>No hypoglycemia</td>
<td>Constipation</td>
<td>$$$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ LDL-C</td>
<td>Triglycerides</td>
<td></td>
</tr>
<tr>
<td>D2 agonists</td>
<td>Bromocriptine</td>
<td>Activates dopaminergic receptors</td>
<td>Alters hypothalamic regulation of metabolism ↑ Insulin sensitivity</td>
<td>0.5%</td>
<td>No hypoglycemia</td>
<td>Dizziness/syncope</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nausea</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Rhinitis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AMPK = adenosine monophosphate–activated protein kinase; ATP = adenosine triphosphate; CKD = chronic kidney disease; CVD = cardiovascular disease; GLP = glucagon-like peptide; D2 = dopamine-2; DPP = dipeptidyl peptidase; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; PPAR = peroxisome proliferator–activated receptor; SB = small bowel.
drug doses signals the need to add another class of oral agent or to transition to insulin therapy. Overall, about 25% of patients reach long-term glucose targets with a sulfonylurea alone; stated another way, three of four patients will require additional modes of therapy. As shown in Table 237-3, advantages of sulfonylureas include low cost (especially with generics), convenience (once-daily dosing), and proven reduction of microvascular end points (retinopathy, nephropathy, and probably neuropathy). Additional disadvantages include hypoglycemia and weight gain.

**Nonsulfonylurea Secretagogues**

Repaglinide and nateglinide are nonsulfonylurea-based drugs that interact with a different portion of the sulfonylurea receptor to stimulate insulin secretion. Their major advantage is their rapid and relatively short duration of action, which may attenuate postprandial glucose excursions and reduce the risk of fasting hypoglycemia. Both drugs require frequent daily dosing and should be taken 0 to 15 minutes before meals. Repaglinide is a somewhat stronger secretagogue than nateglinide and similar to the sulfonylureas in glucose-lowering power, with an expected average HbA₁c, improvement of 1 to 1.5%. Both agents have a favorable side effect profile and typically produce less clinical hypoglycemia than traditional sulfonylureas. As a result, they may be safer in patients with irregular meal schedules or with renal insufficiency (although any secretagogue must be used with great caution as creatinine clearance declines). The primary disadvantages of the nonsulfonylureas are their high cost and multiple dosing schedules and the lack of long-term outcomes data with these agents.

**Biguanides**

Metformin is the only biguanide available for use in the United States. Unlike sulfonylureas, this agent is considered an insulin sensitizer, although its precise mechanism of action is poorly understood. Metformin most likely acts at least in part by reducing hepatic glucose production by suppressing gluconeogenesis. Metformin also augments peripheral glucose disposal, although this effect may be mostly secondary to reversal of glucotoxicity. The drug is a weak activator of adenosine monophosphate–activated protein kinase (AMPK), an enzyme that is usually triggered by adenosine monophosphate, an important intracellular signal of energy stores. Metformin exhibits a glucose-lowering effect similar to that of the sulfonylureas (HbA₁c, off of 1 to 2%). As with sulfonylureas, however, only about one fourth of patients will be adequately controlled with long-term monotherapy. Metformin has a relatively short half-life (it is eliminated exclusively by the kidney) and is therefore given in two or three divided doses with meals. Several extended-release metformin products allow more convenient once-daily dosing.

Because the effects of metformin are extrapancreatic, insulin levels generally fall, which may provide a cardiovascular advantage, as suggested in the UKPDS (see earlier). Other benefits of metformin include mild weight loss, mild (<10%) LDL and triglyceride reductions, and the absence of hypoglycemia when it is used as monotherapy.

Side effects are primarily gastrointestinal, including abdominal pain, bloating, nausea, diarrhea, and anorexia; these may be partially responsible for its mild weight loss effect. Metformin can also very rarely produce lactic acidosis (approximately 0.03 case per 1000 patient years) and should therefore not be given to patients with renal insufficiency (serum creatinine ≥1.5 in males or ≥1.4 in females), liver disease, unstable congestive heart failure, metabolic acidosis, or ongoing alcohol abuse. The drug should also be held in dehydrated patients and in the perioperative setting or the administration of intravenous radiotracers (agents that cause a decline in renal function occurs). Recent observational data sets suggest that the current prescribing guidelines in patients with mild renal insufficiency may be to some extent overly conservative.

**Thiazolidinediones**

Thiazolidinediones (TZDs) reduce insulin resistance, most likely through activation of PPAR-γ, a nuclear receptor that regulates the transcription of several insulin-responsive genes that regulate carbohydrate and lipid metabolism. The biologic effect of TZDs is primarily mediated by stimulation of peripheral glucose metabolism. PPAR-γ activation also attenuates lipolysis and stimulates peripheral fatty acid and ketone body production, thereby redistributing fat stores from the liver and muscle to subcutaneous depots. This effect may be largely responsible for the “insulin-sensitizing” effects of the TZDs. There is a concomitant modulation in the circulating levels of adipocytokines, particularly in adiponectin, which is increased two- to three-fold after TZD therapy. In 1997, troglitazone was the first TZD approved for use in the United States; although effective, the drug was withdrawn from the market 2 years later because of concerns about idiosyncratic hepatotoxicity. Rosiglitazone and pioglitazone were later approved; these agents have no significant hepatotoxicity.

Compared with sulfonylureas and metformin, TZDs, when used as monotherapy, have much lower absorption (0.5% lower in the pioglitazone group, making the impact of the insulin-sensitizing properties of the TZD difficult to know fully. Moreover, an increase in heart failure diagnosis was observed in active therapy patients (see later). These data concerning a potential benefit of pioglitazone on atherosclerosis outcomes need to be confirmed.

The effects of the TZDs on cardiovascular outcomes became even more confusing when in 2007 when a well-publicized meta-analysis was published demonstrating an increase in myocardial infarction events in compiled rosiglitazone studies, each of which was not powered to assess for cardiovascular events and most of which did not adjudicate these outcomes. A subsequent randomized clinical trial (RECORD) did not support the meta-analysis conclusion, indicating for use in patients with New York Heart Association class III and class IV heart failure (see later).

Finally, there is some evidence that TZDs may slow the decline of β-cell function, thus delaying the clinical progression from IGT to overt diabetes mellitus. At the very least, the drugs have been demonstrated to have a more durable effectiveness when compared with sulfonylureas and, to a lesser extent, metformin (ADOPT trial).

A number of other oral hypoglycemic agents, TZDs are more expensive. Side effects of the TZDs are largely related to fluid retention and fat redistribution and include weight gain, edema, mild anemia, and worsening of heart failure. Reports of the development of new heart failure has led to extensive study of this issue. These investigations have concluded that although the risk for heart failure is approximately two-fold compared with non–TZD patients, this appears to result mainly from increased extracellular fluid due to the drug’s effects on sodium handling in the nephron. It is suspected that patients who decompensate on exposure to TZDs likely had previously unrecognized diastolic dysfunction, which is a common phenomenon in older patients with type 2 diabetes, especially in the setting of long-standing hypertension. These drugs are therefore contraindicated for use in patients with New York Heart Association class III or IV heart failure and not recommended in anyone with symptomatic heart failure (i.e., class II). Notably, the side effects of weight gain, edema, and heart failure develop most commonly in patients receiving concomitant insulin therapy.

Recently, the TZDs have also been associated with bone loss and increased bone fracture rates in women. Fractures have tended to occur in peripheral bones, such as the arms, wrists, and lower legs and feet. The mechanism of this effect remains obscure but may involve an effect on stromal stem cells with preferable differentiation into adipocytes instead of osteoblasts. These agents should therefore be used cautiously in women with or at risk for osteoporosis, and routine advice regarding measures to maintain good bone health should be provided.

TZDs should also not be used in patients with active liver disease or with elevated serum transaminases (alanine transaminase ≥2.5 times the upper limit of normal). Periodic monitoring liver function tests based on clinical judgment might be discontinued if transaminases are elevated 1 to 2 times or more the upper limit of normal. Somewhat paradoxically, these agents reduce hepatic fat content and might actually improve the biochemical abnormalities in the liver condition encountered most frequently in obese, type 2 diabetic patients: nonalcoholic steatohepatitis.

**α-Glucosidase Inhibitors**

Acarbose and miglitol are competitive inhibitors of α-glucosidases, brush border enzymes in the proximal small intestine that serve to break down carbohydrates into monosaccharides. Acarbose is predominantly absorbed systemically, whereas miglitol is absorbed and rapidly excreted (unchanged) in the urine. Perhaps as a result of improved glycemic control, both these agents are associated with modest (~10%) reductions in circulating triglyceride levels and have no appreciable effects on LDL or HDL cholesterol.
In controlled trials performed in patients with type 2 diabetes, α-glucosidase inhibitors reduced postprandial glucose excursions and produced small (0.5 to 0.8%) but meaningful reductions in HbA1c. Their most prominent effect is on postprandial blood glucose levels. It has been suggested that the postprandial glucose level may be more closely aligned with cardiovascular risk than is fasting glucose concentration. It is of interest that in a post hoc analysis from the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM diabetes prevention trial), acarbose therapy was associated with a marked reduction (~50%) in the incidence of cardiovascular events in these prediabetic subjects. There have been no long-term studies employing an α-glucosidase inhibitor in diabetic patients, however, to assess whether such a seemingly vasculoprotective effect might be confirmed. These drugs do not lead to any changes in weight.

The most common side effects associated with both acarbose and miglitol are abdominal pain, bloating, flatulence, and diarrhea. These effects have negatively affected their popularity in the United States, although they remain widely used in several overseas countries, including Germany and Japan. The gastrointestinal symptoms can be minimized by initiating therapy at low doses and by using a slowly escalating dose titration schedule. Their use is discouraged in patients with inflammatory bowel disease, colonic ulceration, or any other significant chronic gastrointestinal disorder. They are also to be avoided in patients with advanced liver disease.

**Glucagon-like Peptide-1 Receptor Agonists**

Exenatide and liraglutide are GLP-1 receptor agonists, sometimes referred to as incretin mimetics. They stimulate insulin secretion in a glucose-dependent fashion, inhibit glucagon secretion, slow gastric emptying, and enhance satiety, respectively. These agents are available as a fixed dose of an injectable formulation, either once (exenatide) or twice (liraglutide) daily. This class is approved for use as monotherapy and in combination with oral agents in type 2 diabetes, with an anticipated reduction in HbA1c, of 0.7 to 1.1% compared with placebo. The GLP-1 receptor agonists promote an average weight loss of 4 to 5 kg in long-term studies, but there is considerable variation in the response. This feature distinguishes these agents from current oral antihyperglycemic agents. Moreover, GLP-1 mimetics are not approved for use with insulin. Side effects include nausea and vomiting, but these effects tend to wane with time. Acute pancreatitis, including hemorrhagic forms, has been reported in patients taking GLP-1 agonists, but it remains unknown whether these cases actually resulted from the drug because this complication is in general more commonly seen in the patient population. These agents do not by themselves lead to hypoglycemia but may increase the risk when used with insulin secretagogues. In preliminary studies in rodent models, incretin mimetics appear to preserve β-cell function and therefore might be useful earlier in the disease course than is currently recommended. At present, however, exenatide may be considered an alternative to the initiation of insulin for those patients whose treatment with oral agents is failing, although they are increasingly popular earlier in the disease course. Other incretin mimetics under active development include several injectable long-acting GLP-1 agonists that can be given weekly.

**Dipeptidyl Peptidase-4 Inhibitors**

Members of this class (e.g., sitagliptin, saxagliptin, vildagliptin) inhibit the activity of DPP-4, the enzyme responsible for the breakdown of the naturally occurring incretins, GLP-1 and glucose-dependent insulinotropic peptide (GIP). As monotherapy and in combination with other oral agents, glitazins reduce HbA1c by 0.5 to 0.8% versus placebo therapy. However, because the baseline HbA1c, in these trials (8 to 8.5%) was lower than in most studies previously conducted with more traditional agents, it is difficult to compare the results. In head-to-head comparisons, the glitazins appear to fare favorably to most other available oral antihyperglycemic medications. The advantage of this therapeutic class is the relative absence of reported major side effects, including lack of hypoglycemia and weight neutrality. They may be of greatest use in patients with mild elevations of blood glucose. The DPP-4 inhibitors are currently approved for use as monotherapy and in combination with other drugs except for insulin and GLP-1 agonists (see later). There are no data on microvascular or macrovascular outcomes. DPP-4 inhibitors are relatively inexpensive and the long-term safety of DPP-4 inhibition is not known. For example, angioedema, Stevens-Johnson syndrome, and acute pancreatitis have been reported, but it is not clear whether there is a causative relationship to any of these events.

**Bile Acid Sequestrants**

The cholesterol binding resins are drugs that can be used for the treatment of hyperlipidemia. However, they are significantly less effective than statins, and these drugs have been relatively unpopular among patients owing to their gruity consistency, high doses required for an effect, and frequent constipation. Recently, one member of this class, colestevam, has been approved for use as monotherapy and in combination with other antihyperglycemic drugs for patients with type 2 diabetes. Its mechanism of action remains poorly understood but might involve modulation of the incretin system. It likely does not reduce carbohydrate absorption. HbA1c, efficacy is mild, with reductions in the 0.5% range. Benefits include a generally nonsystolic pharmacologic profile and concurrent reduction of LDL cholesterol. It is weight neutral. All bile acid sequestrants can increase triglycerides, and colesvelam is specifically contraindicated in patients with levels above 500 mg/dL and in those who have had pancreatitis related to hypertriglyceridemia. It is also contraindicated in patients with a history of bowel obstruction and should generally not be used in anyone with a significant history of gastrointestinal disease.

**Dopamine-2 Receptor Agonists**

Dopamine agonists have been studied for their mild antihyperglycemic effects (HbA1c, reduction, 0.3% or less) for years. Bromocriptine, an ergot derivate, available since the 1970s to treat hyperprolactinemia and Parkinson’s disease, is recently approved in low dose as a glucose-lowering agent in type 2 diabetes. Its mechanism of action is not well understood but may involve alteration of the hypothalamic neurotransmitter milieu, with systemic effects on free fatty acid oxidation and hepatic glucose production. It is weight neutral and not associated with hypoglycemia. Potential side effects include hypokalemia, dizziness, syncope, exacerbations of psychiatric disorders, somnolence, and nausea. Bromocriptine should not be used in patients taking dopamine antagonists.

**Insulin Therapy in Type 2 Diabetes**

The principles of insulin therapy and details of insulin preparations, regimens, and monitoring are discussed in the previous chapter on type 1 diabetes (Chapter 236). Insulin is commonly used as first-line therapy for nonobese, insulin-requiring, type 2 diabetes patients and is often temporarily required during times of severe stress (e.g., injury, infection, surgery) or during pregnancy. Insulin should not be used as first-line therapy for patients who are poorly compliant, unwilling to self-monitor glucose levels, or at high risk for hypoglycemia (e.g., very elderly patients). In obese patients, problems with insulin resistance often necessitates the use of large doses of insulin, which can interfere with efforts to restrict calorie intake and achieve weight loss. In leaner patients and in patients with relatively mild fasting hyperglycemia (who continue to maintain endogenous insulin secretory capacity), relatively small doses of basal insulin (e.g., 0.3 to 0.4 U per kilogram of body weight per day) given once or twice per day may be sufficient to achieve glucose targets. Many of these patients retain some degree of meal-stimulated endogenous insulin secretion and may therefore require no or less rapid-acting insulin as well.

Although a common practice has been to administer a single dose of NPH insulin in the morning, the glucose-lowering effect of this regimen does not last long during a 24-h period. Because a successful insulin treatment is to counteract accelerated rates of endogenous glucose production in the morning, it is generally more effective to split the dose and to administer sufficient amounts of intermediate-acting insulin in the evening (preferably at bedtime) to optimize control. Alternatively, premixed insulins containing 70 to 75% NPH and 25 to 30% of a short- or rapid-acting insulin (e.g., regular human insulin, lispro, or aspart) can be given twice daily. Although somewhat inflexible because of their combined contents in fixed ratios, these insulins provide a level of convenience for some patients who are not able or willing to mix insulins or use strategies involving three or four injections per day. With the availability of long-acting, basal insulins over the past decade, such as glargine and detemir, one injection per day is an increasingly favored approach in many patients. This may be combined with oral glucoselowering agents to facilitate endogenous insulin release and action. Typically these agents are offered at bedtime, but they can actually be administered at any time of day. In patients taking large doses or in whom it is suspected that the hypoglycemic effect is waning before 24 hours (as is more commonly seen with detemir), twice-daily dosing can be used.

With regard to the initiation of even more advanced insulin replacement regimens, which are required in certain insulin-deficient type 2 patients (and are similar to the optimal regimens in type 1 patients), there are several acceptable approaches. The optimal insulin strategy in type 2 diabetes is not clear. In general, the more insulin injections, the tighter the control, but this must be balanced against convenience. In many patients this may be combined with oral glucoselowering agents to facilitate endogenous insulin release and action. Typically these agents are offered at bedtime, but they can actually be administered at any time of day. In patients taking large doses or in whom it is suspected that the hypoglycemic effect is waning before 24 hours (as is more commonly seen with detemir), twice-daily dosing can be used.

When considering the addition of even more insulin, it seems that the goal of therapy is to divide the total daily dose evenly, with two thirds given before breakfast and the remaining third before dinner. Each of the two doses is then further subdivided: at breakfast, one third of the dose is given as intermediate-acting insulin and the other third as a short- or rapid-acting preparation; at dinner, the dose is divided into two equal parts. As an example, for a 90-kg man with estimated requirements of 0.67 U/kg/day, 60 U of insulin may be required. By use of this method, the patient might receive 27 units of NPH with 13 units of regular insulin or a rapid-acting insulin analogue (e.g., lispro, aspart, or glulisine) before breakfast, then 10 units of NPH with 10 units of analogue before dinner. More refined “basal-bolus” regimens using more modern insulins offer more physiologic insulin replacement. The regimen in the most motivated and capable patients is ideally adjusted on the basis of the anticipated carbohydrate intake (“carbohydrate counting”) as well as the before-meal blood glucose level. These
regimens are more complex and require frequent dosage adjustments and more intensive glucose monitoring. In the absence of hyperglycemic complications, clinicians should generally begin with more conservative doses of insulin to minimize hypoglycemia and to smooth the patient's transition to multiple-dose subcutaneous insulin therapy. In short, the complexity of the regimen should be individualized according to the clinical context, the patient's acceptance and capabilities, and the physician's education and motivation.

The Treatment-To-Target in Type 2 Diabetes (4-T) trial compared glycemic outcomes from various insulin regimens in more than 700 patients whose diabetes was inadequately controlled despite therapy with metformin and sulfonylurea. The participants were randomized to (1) premixed insulin analogues twice a day (aspart 70/30 before breakfast and supper), (2) prandial rapid-acting insulin analogue (insulin aspart) three times daily, or (3) a basal insulin analogue (insulin detemir) once (or twice) daily, with the goal of achieving an HbA1c level of 6.5% or less. After 1 year, the HbA1c was not at target, the sulfonylurea was discontinued and a second type of insulin initiated. For those on the premixed regimen, once-daily aspart was added before lunch; for those on the prandial-only strategy, once-daily basal analogue was added; and for those using basal insulin alone, the regimen was advanced to incorporate three times per day prandial rapid insulin. At 3 years, the median HbA1c across groups was 6.9% (premixed, 7.1%; prandial, 6.8%; basal, 6.9%); however, almost three in four patients required two types of insulin in combination. More patients who had started therapy with a basal insulin only (43.2%) or a prandial insulin only (44.8%) achieved target than those initially randomized to the premixed (31.9%). Weight gain amounted to 3.6 kg, 5.7 kg, and 6.4 kg in the basal, premixed, and prandial groups, respectively. Less hypoglycemia occurred in those randomized to the basal insulin approach (1.7 per patient-year) than the premixed (3.0 per patient-year) or prandial (5.7 per patient-year) insulin regimens. These findings provide support for treatment to begin with basal insulin once a day, and then add mealtime insulin if glycemic targets are not met. However, in patients not able to handle more complex regimens, premixed insulin twice daily is a reasonable option as well. Experience with the use of intensified insulin treatment, including continuous subcutaneous insulin infusion pumps and multiple subcutaneous injection regimens, is growing in patients with type 2 diabetes. Preliminary results suggest that intensified treatment may be successfully applied to selected patients.

In many cases, the combination of intensive insulin therapy with oral hypoglycemic agents (e.g., TZDs or metformin) may reduce insulin dose requirements and improve glycemic control. Although this is growing in acceptance, the potential benefit of reducing circulating insulin levels (by combination therapy) on the development of atherogenesis remains to be established. As in patients with type 1 diabetes, weight gain and hypoglycemia are potential side effects of insulin therapy. It is noteworthy, however, that the incidence of severe hypoglycemia is markedly lower (<5%) than that seen in patients with type 1 diabetes.

Pramlintide

See Chapter 236 for a brief description of this newer agent, which is also approved for insulin-requiring patients with type 2 diabetes.

Treatment Strategies for Type 2 Diabetes

In contrast to type 1 diabetes, in which insulin therapy is required, many pharmacologic options exist for the management of type 2 diabetes. The pros and cons of the various oral hypoglycemic agents have been discussed; often, it is difficult to justify the use of one oral agent over another, although the general consensus of endocrinologists is to recommend metformin as first-line therapy in the absence of contraindications, given its effectiveness, the lack of hypoglycemia associated with its use as monotherapy, its low cost, and weight neutrality. It is now believed that in most cases metformin therapy should be initiated early, is concurrent with lifestyle intervention, and is gradually increased to the maximally effective dose over 1 to 2 months. In the event these interventions fail to achieve the glycemic goals set for the patient within about 3 months, another drug should be added to the regimen (Fig. 237-4). What the next step should be is much more controversial and remains uncertain. Most studies comparing oral drugs have focused on glycemic end points, and whereas low/modest exceptions may exist, there have been no oral agents that have compared drugs for more relevant clinical outcomes such as mortality or microvascular and macrovascular complications. To date, the largest study to address such outcomes in type 2 diabetes was the UKPDS. In the UKPDS, the long-term follow-up of the study participants assigned to more intensified therapy demonstrated improved outcomes for microvascular complications and a trend toward reduced mortality for those assigned insulin and sulfonylureas (as well as metformin). The ability of the study to detect differences among the different treatments was limited because of drug cross-overs and the frequent need for drug combinations as the study progressed. On the other hand, the long-term benefits of newer antidiabetic agents have not yet been established, once again highlighting the importance of ongoing research.

The choice of second-line pharmacologic therapy for type 2 diabetes should be influenced in part by the severity of fasting hyperglycemia, the presence and magnitude of hyperglycemic symptoms, and the degree of obesity. Other factors such as age, comorbid conditions, propensity to certain side effects, drug cost, and convenience should also be considered. Published clinical trials comparing drug combinations with monotherapy have generally shown additive reductions in HbA1c; with fewer exceptions, the magnitude of Hba1c reduction approximates that achieved when the added agent is used as monotherapy. As is the case with monotherapy, there is no convincing evidence favoring one combination regimen over another, and most combinations have been approved by the FDA. Triple therapy, or combining three agents to achieve glycemic targets, is also used in clinical practice (although not formally with FDA approval) and appears to be effective. Ultimately, if glucose targets cannot be met by combining oral agents, insulin remains an effective treatment option.

Two published algorithms include one from a consensus group representing the ADR and the ADA (see Nathan in Suggested Readings) and one from the American Association of Clinical Endocrinologists/American College of Endocrinology (Rodbard in Suggested Readings).

Monitoring

See Chapter 236 for details. Patients with type 2 diabetes generally require less frequent self-monitoring of blood glucose concentration, particularly those managed with oral agents or less intensive insulin regimens. Glucose and Hba1c targets should be the same as in type 1 diabetes (see Table 237-4), with the recently appreciated caveat that older patients (>65 to 70 years) may not benefit from more stringent goals, especially in the setting of long disease duration (>12 years) or significant underlying risk for or overt cardiovascular disease. Importantly, each patient’s desirable glucose range may be an individual decision between the practitioner and the patient. Elements of this decision must take into account the motivation and capabilities of the patient, propensity for hypoglycemia, and its unawareness, presence or absence of complications, and, of course, other established comorbidities.

Inpatient Management of Diabetes

Much attention has been paid recently to the inpatient management of hyperglycemia, both in patients with newly diagnosed diabetes and in those whose glucose elevations are a response to illness. Observational studies previously have correlated the degree of hyperglycemia and outcomes in a variety of settings, including after cardiac surgery, in the critically ill, and in patients with acute myocardial infarction and stroke. Acutely, hyperglycemia has a notable detrimental effect on the immune system, wound healing, endothelial function, and cardiac metabolism. When glucose elevations are severe, dangerous fluid shifts and electrolyte fluxes may occur. However, multiple studies have failed to confirm a benefit from aggressive control of inpatient glucose levels, and studies have actually raised the probability of increased mortality risk from aggressive control of inpatient glucose levels when intensive continuous intravenous insulin therapy targets a blood glucose level lower than 108 mg/dL. These adverse effects have occurred in the setting of (but are not clearly the result of) a several-fold increase in the risk for severe hyperglycemia. Whether there is any short-term benefit of tight glucose control in noncritically ill hospitalized patients is unknown because adequate clinical trials have not been conducted in this setting.

Reasonable approaches to both these patient groups have been proposed by the ADR, the American Association of Clinical Endocrinologists (AAACE), and the American College of Physicians with current targets set at 140 to 180 mg/dL using intravenous insulin in the intensive care setting, and maintaining preprandial blood glucose levels lower than 140 mg/dL in other patients. As in the outpatient arena, individualization is important; patients with severe comorbidities or with short life expectancy can be reasonably kept at a more conservative range. Multidisciplinary inpatient diabetes management teams have been shown to be useful in assisting hospitals to improve the quality of their diabetes care and in reducing the length of stay of diabetic patients.
With our increasing understanding of the pathogenesis of type 2 diabetes and our appreciation of the often lengthy period between impaired glucose metabolism and overt diabetes, there has been significant attention directed to the possibility of preventing this disease in at-risk individuals.

In the Diabetes Prevention Program, more than 3000 overweight subjects with IGT were randomized into four treatment arms: (1) intensive lifestyle changes aimed at reducing body weight by 7% through a low-fat diet and 150 minutes of weekly exercise; (2) treatment with metformin, 850 mg twice per day; and (3) treatment with placebo pills, twice per day. The last three groups also received standard information about diet and exercise. The trial was stopped a year early because of definitive results. In the placebo group, 29% of patients developed diabetes during the average follow-up period of 3 years, compared with 22% of patients taking metformin and only 14% of patients undergoing intensive diet and exercise. The relative risk reduction for patients taking metformin was 31% versus standard care, whereas patients undergoing intensive lifestyle interventions reduced their risk by an impressive 58%. This risk reduction was identical to that measured by Finnish investigators in the Diabetes Prevention Study, involving a similar study design but focusing on lifestyle change alone. This suggests that patients with IGT can sharply lower their immediate risk for diabetes with intensive lifestyle changes (or in some cases with metformin).

Whether screening, identifying, and then treating patients with IGT in routine clinical practice is cost-effective or even doable remains somewhat controversial. Certainly, if recommendations regarding healthy lifestyle changes were followed by high-risk patients, the incidence of type 2 diabetes would decrease. If such therapy is durable, this would necessarily translate to fewer microvascular complications over time. Whether such interventions will mitigate the risk for macrovascular disease is less clear, although Diabetes Prevention Program participants on diet and exercise did experience some amelioration in cardiovascular risk factors.

How drug therapy fits into this equation is similarly a point of controversy. Notably, after metformin therapy was washed out in Diabetes Prevention Program participants for 2 weeks, 25% of those whose diabetes was apparently prevented developed the disease. Similarly, in the STOP-NIDDM diabetes prevention trial involving the α-glucosidase inhibitor acarbose, a 25% decrease in the appearance of type 2 diabetes during a 3-year period was demonstrated. In two studies involving TZDs, larger risk reductions have been observed. In DREAM, rosiglitazone therapy reduced the progression to diabetes in high-risk patients by 62%, and in the ACT NOW trial, pioglitazone was associated with an 81% risk reduction. Moreover, pioglitazone has recently been reported to diminish carotid intimal thickening by 38% in patients with IGT in a multicenter clinical trial. Importantly, no drug is currently approved by the FDA for diabetes prevention, although metformin is used not uncommonly in such efforts.

A consensus statement from the ADA and the EASD has endorsed lifestyle change in anyone identified with a prediabetic state. It also advised the consideration of metformin therapy in those at especially high risk, such as individuals with both IFG and IGT, combined with other high-risk features such as family history and characteristics that predict an effective response to metformin, based on the DPP. The latter include age younger than 60 years, body mass index greater than 35 kg/m², and fasting plasma glucose level of 110 mg/dL or higher. An approach that emphasizes healthy lifestyle changes is likely more cost-effective and accompanied by other health benefits than one focused on pharmacotherapy. With now more than 50 million individuals in the United States considered to be at high risk for developing diabetes, the economic implications of any broad recommendations will need careful consideration.

**Acute Metabolic Complications**

**Diabetic Ketoacidosis**

See Chapter 236 for a discussion of diabetic ketoacidosis.

**Hyperosmolar Hyperglycemic Syndrome**

**Clinical Manifestations**

The metabolic state formerly known as the hyperglycemic hyperosmolar nonketotic state or coma has been renamed the *hyperosmolar hyperglycemic syndrome* (HHS) to highlight two important points: (1) ketosis (and acidosis) may be present to varying degrees in HHS, and (2) alterations in sensoium most commonly occur in the absence of coma. In fact, only 10% of HHS patients present with frank coma, and an equal percentage show no signs whatsoever of mental status change.

As shown in Table 236-6 in Chapter 236, the hallmarks of the HHS are severe hyperosmolarity (>320 mOsm/L) and hyperglycemia (>600 mg/dL). Severe hyperglycemia occurs because patients cannot consume enough liquid to keep pace with a vigorous osmotic diuresis. The resulting impairment in renal function eventually further reduces glucose excretion through the kidney, leading to remarkable blood glucose elevations, sometimes exceeding 1000 mg/dL. In contrast to diabetic ketoacidosis, even though glucose concentrations are generally higher, severe acidosis and ketosis are generally absent in the HHS. This is probably explained by the residual insulin secretion capacity retained by patients with even several decades of type 2 diabetes. That is, their insulin levels remain sufficient to suppress lipolysis and to avoid significant keto acid production. However, some type 2 patients with depressed endogenous insulin secretion may be unable to suppress ketone production fully in the face of elevated counter-regulatory hormones produced by physical illness. Because HHS patients have higher portal ven insulin concentrations than do patients with diabetic ketoacidosis, keto acid production by the liver is relatively mild, yielding only mild acidosis. In the HHS, in the absence of concurrent acid-base disturbances, arterial pH rarely drops below 7.30, and serum bicarbonate levels typically do not fall below 18 mEq/L.

In the hyperosmolar hyperglycemic state, clinical severity and levels of consciousness generally correlate with the severity and duration of hyperosmolarity. Clinical signs indicate profound dehydration; gastrointestinal symptoms are seen less frequently than in diabetic ketoacidosis. A variety of often reversible neurologic abnormalities may exist, including grand mal or focal seizures, extensor plantar reflexes, aphasia, hemisensory or motor deficits, and worsening of a preexisting organic mental syndrome. The laboratory picture is dominated by the effects of uncontrolled diabetes and dehydration; renal function is impaired, hemoglobin and hematocrit are elevated, and liver function test results may be abnormal because of baseline hepatic steatosis. Although severe hyperglycemia would be expected to lower measured serum sodium concentration, it is not uncommon to see normal or even elevated sodium levels because of the severity of dehydration. The serum osmolarity can be measured directly or estimated by the following formula, which excludes urea because it is freely diffusible throughout the body and therefore has little influence on the osmotic pressure gradient:

\[
\text{Effective osmolality (mOsm/L)} = \frac{2\text{[measured serum Na}^+\text{(mEq/L)] + [glucose (mg/dL)/18]}}
\]

**Treatment**

Patients with HHS should be treated as aggressively as are those with diabetic ketoacidosis, although those with the former tend to have more dramatic volume contraction (Chapter 236). By definition, acidosis is not present or is minimal in degree. Accordingly, patients may not require the coadministration of dextrose along with insulin, as is recommended in patients with diabetic ketoacidosis to allow ketones to clear and the acidosis to resolve. Also, it is important to volume-resuscitate the patient adequately before insulin is administered for fear that intracellular fluid shifts that occur as glucose levels are reduced may worsen systemic tissue perfusion. Because, by definition, there is no significant acidosis to clear in HHS, patients may be transitioned directly from insulin infusion to subcutaneous injections, without need for any coadministration of dextrose as is necessary in diabetic ketoacidosis to allow further clearance of ketone bodies. Some patients with HHS may ultimately be able to be managed with oral agents alone. However, the development of HHS signifies a significant degree of insulin deficiency. As a result, it is always best to prescribe insulin injections before the patient is discharged and to reserve judgment about the appropriateness of oral agents until the patient’s progress can be monitored and reassessed in the outpatient setting.
insulin resistant and therefore less likely to develop abnormally low blood glucose levels even when taking insulin injections. Perhaps more important, type 2 patients are more commonly treated with oral agents than with insulin. Many of these drugs reduce glucose levels through nonpancreatic mechanisms and therefore do not predispose to hypoglycemia when they are used as monotherapy or in combination with each other. On the other hand, severe hypoglycemia may be less well tolerated by the aging brain, and therefore it needs to be scrupulously avoided, particularly in elderly patients and especially given the recent clinical trial evidence of an association between hypoglycemia and increased cardiovascular mortality in those at high cardiovascular risk.

### CHRONIC DIABETIC COMPLICATIONS

The pathogenesis of the microvascular and neuropathic complications of diabetes is discussed in Chapter 236. Patients with both forms of diabetes are at risk for retinopathy, nephropathy, and nerve dysfunction.

#### Atherosclerosis

Atherosclerosis (Chapter 70) involving the coronary, cerebral, and peripheral (lower extremity) arteries is the predominant cause of diabetes-related mortality, responsible for up to 70% of all deaths in patients with this disease. The atherosclerotic process in diabetes is essentially indistinguishable from that of the nondiabetic population, but it begins earlier and is often more extensive and more severe. A predilection to cardiovascular disease is observed over the entire spectrum of diabetes, from poorly controlled insulin-dependent patients to those with mild, diet-controlled hyperglycemia. For unclear reasons, the disparity between diabetic and nondiabetic persons is more pronounced in women. When diabetes is accompanied by other major cardiovascular risk factors such as hypertension, dyslipidemia, and smoking, diabetes markedly augments the incidence of macrovascular complications. For example, the observed 2- to 3-fold greater risk for myocardial infarction with diabetes rises to 8-fold in the presence of hypertension and to nearly 20-fold if both hypertension and dyslipidemia are present; smoking increases these risks even further. As a result, the diagnosis of diabetes mellitus should lead to a careful review of coexisting and compounding cardiovascular risk factors and the initiation of aggressive preventive measures.

Diabetes is an independent risk factor for accelerated atherosclerosis. Its association with vascular disease is not solely attributable to an increased prevalence of other recognized vascular risk factors, such as hypertension and dyslipidemia. Many abnormalities induced by the diabetic state may contribute to atherosclerosis, including lipid abnormalities (e.g., increased total VLDL and LDL, increased small dense [atherogenic] LDL, decreased HDL, increased lipoprotein oxidation, increased lipoprotein glycosylation, decreased lipoprotein lipase activity), accentuated platelet aggregation and adhesion, endothelial cell dysfunction, and induced procoagulant state (e.g., increased clotting factors and fibrinogen; decreased levels of antithrombin III, protein C, and protein S; and decreased fibrinolytic activity). It has been suggested that hyperinsulinemia per se may contribute to macrovascular disease; proposed pathogenetic mechanisms include insulin-induced stimulation of vascular endothelial and smooth muscle cells, enhanced insulin-like growth factor-I expression, and augmented synthesis of atherogenic factors such as endothelin and plasminogen activator inhibitor. Moreover, insulin resistance appears to be an independent risk factor for vascular events and may exert its effect through many of these disease intermediaries.

Outcomes after cardiovascular events, including myocardial infarction, revascularization, and heart failure, are worse in those with than without diabetes. For example, compared with the general population, a higher proportion of diabetic patients die within a year of an acute myocardial infarction. Accordingly, aggressive management of cardiovascular risk factors is even more imperative in those with diabetes. After myocardial infarction, particularly in the setting of left ventricular systolic dysfunction, β-blockers and angiotensin-converting enzyme (ACE) inhibitors (or angiotensin II receptor blockers [ARBs]) likely offer additional benefits. Although angio- plasty is often a viable option in diabetic patients with coronary disease, there is evidence to suggest that diabetic patients may derive greater than expected comparative benefit from coronary bypass procedures. However, with the recent development of advanced stenting procedures and the use of drug-eluting stents, which attenuate stent restenosis rates, this distinction might become less important. The Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial examined the relative value of prompt revascularization versus initial medical therapy (followed by revascularization as clinically indicated) in patients with type 2 diabetes and stable coronary artery disease. Overall outcomes were essentially equivalent between groups. However, in the predefined stratum of patients who were referred for coronary artery bypass graft (CABG) surgery, the rate of major cardiovascular events was significantly lower with revascularization (22.4%) than with medical therapy (30.5%, *P* = .01). These data suggest that in diabetic patients with ischemic heart disease, prompt bypass surgery may be advantageous compared with medical therapy. In less severely affected patients for whom percutaneous coronary intervention is being advised, a more conservative approach with aggressive, evidence-based attention to cardiovascular risk factor reduction is very reasonable. Obviously, individualization of recommendations is important, directed by a skilled cardiology consultant.

Low-dose aspirin therapy (81 to 325 mg/day) has been routinely recommended for most adult patients with diabetes (especially with concurrent coronary artery disease) because of evidence of reduction in cardiovascular morbidity and mortality in the general population. More recent studies and meta-analyses have not confirmed a major benefit in all patients with diabetes. As a result, the ADA in conjunction with the American Heart Association and the American College of Cardiology have recently downgraded the recommendations for prophylactic aspirin. For primary prevention, aspirin (75-162 mg/day) is now advised in diabetic patients at increased cardiovascular risk, defined as a 10-year risk in excess of 10%, including men older than 50 years and women older than 60 years who have at least one additional major risk factor, such as family history, hypertension, smoking, dyslipidemia, or albuminuria.

Whether asymptomatic patients with diabetes should be routinely screened for coronary artery disease remains controversial. A study showed that the observed 2- to 3-fold greater risk for myocardial infarction with diabetes rises to 8-fold in the presence of hypertension and to nearly 20-fold if both hypertension and dyslipidemia are present;-smoking increases these risks even further. As a result, the diagnosis of diabetes mellitus should lead to a careful review of coexisting and compounding cardiovascular risk factors and the initiation of aggressive preventive measures.

Unfortunately, the known association between diabetes mellitus and premature atherosclerosis may be the only “tip of the iceberg” with regard to linking glucose metabolism and vascular risk. Insulin resistance (i.e., impaired insulin-stimulated glucose metabolism) is common in “healthy” people living in Western nations; in such individuals, insulin resistance is often counterbalanced by increased insulin secretion, preventing the emergence of overt diabetes mellitus. Although this state of insulin resistance and chronic hyperinsulinemia may successfully defend against diabetes, this may come at a separate metabolic cost, with potentially adverse effects on other insulin-responsive systems, such as sympathetic nervous system activity, renal sodium reabsorption, hepatic triglyceride synthesis, vascular endothelial function, and cellular events that mediate the atherosclerotic process, including arterial smooth muscle proliferation, expression of vascular adhesion molecules, matrix metalloproteinases, and a variety of cytokines and chemokines that appear to accelerate atherogenesis. This much is known: nonobese, nondiabetic individuals with insulin resistance have higher blood pressure, glucose concentration, and triglyceride levels (and lower HDL cholesterol concentrations) than those of matched subjects with normal insulin levels. The term metabolic syndrome is used by some to describe this phenomenon, namely, the clustering within one person of hyperinsulinemia, mild glucose intolerance, dyslipidemia, and hypertension, each of which is probably an independent risk factor for atherosclerosis. Whether identifying such individuals as having metabolic syndrome as opposed to treating the composite risk factors individually is of any benefit remains controversial. Prospective population studies have confirmed that chronic hyperinsulinemia predicts the development of cardiovascular disease. Although such statistical associations do not prove causality, they suggest that insulin resistance may play some role in promoting atherosclerosis. If true, this hypothesis further underscores the importance of lifestyle changes in the treatment of type 2 diabetes and suggests that proper diet and exercise could also benefit insulin-resistant patients with more subtle metabolic abnormalities (i.e., metabolic syndrome, IGT, and IFG). The answer to the obvious question of whether
insulin-sensitizing drugs decrease atherosclerosis risk in this setting remains unknown. The aforementioned BARI 2D study additionally explored this question, in patients with established diabetes. In addition to differing approaches to their coronary disease, patients were also randomized to two distinct approaches to their glycemic control. The first focused on insulin provision therapy, with sulfonylureas and insulin, whereas the second consisted of insulin sensitizers, using metformin and rosiglitazone. This aspect of BARI 2D presented some challenges, including an expected crossover between groups in a substantial proportion of patients. Overall, there was no mortality benefit in those assigned originally to the insulin sensitizer strategy. However, there was a strong, but not significant, trend toward less major cardiovascular events in the patients assigned to insulin sensitizers who were randomized to the revascularization group and were in the stratum of patients referred for CABG. This group most likely included the highest-risk patients. Most would agree that, in light of the background scientific underpinnings of an association between insulin resistance and atherosclerosis in preliminary findings from clinical trials, further investigation is warranted to understand better whether improving insulin sensitivity is a worthwhile pursuit, in both patients with and without diabetes.

**ASSOCIATED CONDITIONS**

The prevention of cardiovascular disease in type 2 diabetes requires a comprehensive and multifactorial approach. Such an approach has been shown to reduce cardiovascular events by almost 50% (Steno-2 study). Two cardinal areas for prevention concern the management of hypertension and dyslipidemia. Figure 237-5 shows a theoretical scheme that links insulin resistance and the metabolic syndrome with cardiovascular disease. The reader is referred to the online version of this chapter and to Chapters 67 and 213 in this text for a more detailed discussion of these topics.

**Hypertension**

In patients with diabetes, systemic hypertension (Chapter 67) is an important cofactor in the development of cardiovascular disease, nephropathy, and retinopathy. The prevalence of hypertension in type 2 patients is more than twice that of the nondiabetic population, largely related to the clustering of both disorders in patients with obesity and insulin resistance. Type 1 patients, in contrast, are usually normotensive in the absence of renal disease; if nephropathy develops, most affected patients will then develop secondary hypertension. The importance of aggressive blood pressure management in diabetes has been established by the UKPDS (see earlier); in the study, blood pressure reduction (with ACE inhibitors or β-blockers) in type 2 diabetic patients with hypertension produced striking decreases in both cardiovascular and microvascular outcomes. Subsequent prospective trials, including the Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe (Syst-Eur) trial, and the Hypertension Optimal Treatment (HOT) trial, have confirmed the value of aggressive blood pressure goals in reducing major cardiovascular events in diabetic patients. On the basis of these and other studies, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) has established blood pressure targets of less than 130/80 mm Hg for patients with diabetes mellitus; even stricter reductions (<125/75 mm Hg) are recommended in the presence of established nephropathy. More recently, the ACCORD Study Group reported that targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of composite outcome of fatal and nonfatal major cardiovascular events in patients with type 2 diabetes.

The choice of antihypertensive agent for diabetic patients has for years been the subject of considerable research and debate. Among the various therapeutic options, ACE inhibitors and ARBs may offer special advantages; they have consistently demonstrated the ability to lower intraglomerular pressures and to slow the progression of albuminuria and diabetic nephropathy. These drugs are advocated by the ADA as first-line agents, including their use in normotensive diabetic patients with albuminuria. JNC 7 has additionally endorsed low-dose diuretics, β-blockers, and calcium-channel blockers as preferred agents in diabetic patients with hypertension. β-Blockers should also be strongly considered in the setting of concurrent cardiovascular disease, including prior myocardial infarction, mild to moderate congestive heart failure, and cardiac arrhythmias. There is some clinical trial data to suggest that these agents may be associated with a slightly increased risk for diabetes, possibly related to effects on insulin secretion or the promotion of insulin resistance. They are typically not, however, associated with deterioration in glycemic control. β-Blockers may blunt the adrenergic response to hypoglycemia. Accordingly, they should be used with caution in any patient with frequent hypoglycemic episodes, especially if hypoglycemia is already manifest. Prospective trials comparing antihypertensive agents in diabetic patients have yielded mixed results. In the UKPDS, β-blockers were as effective as ACE inhibitors in reducing adverse cardiac and microvascular outcomes. Conversely, several large trials, including the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the Captoril Prevention Project (CPP), the Heart Outcomes Prevention Evaluation (HOPE) study (MICROHOPE substudy), and the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET), suggest improved cardiovascular outcomes with the specific use of ACE inhibitors as first-line therapy. On the basis of currently available evidence, ACE inhibitors are recommended as first-line antihypertensive therapy in patients with diabetes, especially in the presence of microalbuminuria or overt nephropathy. ARBs are an excellent alternative, especially in patients who are unable to tolerate ACE inhibitors because of cough.

**Dyslipidemia**

Dyslipidemia (Chapter 213) is another critical therapeutic target in the management of diabetes. The most common lipid disorder associated with diabetes is an increased level of triglyceride-rich lipoproteins (e.g., VLDL), low levels of HDL, and the presence of small, dense, and, as a result, more atherogenic LDL particles. The third report of the National Cholesterol Education Program (NCEP) Adult Treatment EPan (ATP III) continues to identify LDL cholesterol as the primary target for therapy on the basis of overwhelming evidence from clinical trials. This panel has established diabetes as a coronary heart disease “equivalent,” meaning that all diabetic patients should strive for LDL levels below 100 mg/dL. In addition, HDL levels should exceed 40 mg/dL (50 mg/dL in women); triglyceride levels should fall below 150 mg/dL.

Recommendations from the ADA are similar. Both organizations endorse more aggressive LDL reduction (to below 70 mg/dL) in high-risk patients with overt cardiovascular disease. Such a target is based on the findings of randomized clinical trials in patients with known coronary artery disease. In diabetic patients with multiple additional cardiovascular risk factors, an optional goal of less than 70 mg/dL can also be considered. There is also now widespread agreement that LDL reduction should be considered part of standard diabetes management in virtually all adults older than 40 years irrespective of the baseline LDL cholesterol level, unless it is already extraordinarily low or if contraindications to such therapy are present.

Hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors (i.e., statins) are generally used as first-line therapy for lowering LDL cholesterol in patients with diabetes; of note, many of the statins at high doses have a modest triglyceride-lowering effect as well. Randomized clinical trials involving diabetic patients alone (Collaborative Atorvastatin Diabetes Study [CARD5], diabetic subset of the Heart Protection Study) have confirmed equal if not greater benefit of statin therapy in this important subgroup of patients. If statins are contraindicated or poorly tolerated, nicotinic acid
(niacin), a bile acid sequestrant (“binding resin,” e.g., cholestyramine, colesti-
pol, colesvelam), or a cholesterol absorption inhibitor (e.g., ezetimibe), can be used to lower LDL. It should be noted that the value of the latter in reduc-
ing cardiovascular disease is not established. Niacin, although it is also effec-
tive at lowering LDL (and triglycerides), may be less useful in diabetic patients because it can worsen insulin resistance and adversely affect glycemic control. Also, the binding resins are generally poorly tolerated and may increase triglycerides. Achieving some of the more stringent LDL targets noted earlier may require combination therapy with a statin plus one of these drug classes. Which to add remains controversial. Recently, a lack of effect of ezetimibe on direct measures of atherosclerosis (by carotid or intravascular ultrasound) has been found. Randomized clinical trials examining actual cardiovascular events with this drug are still under way. The ACCORD study group recently reported that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone in patients with type 2 diabetes.\footnote{Particularly given all these concerns, patients should have their statin titrated aggressively first before any consideration of combi-
nation therapy is made.}

Although most published trials involving diabetic patients involve statins to lower LDL, the characteristic lipid profile in the diabetic patient is an elevated triglyceride concentration and low HDL cholesterol, both risk factors for coronary artery disease. Initial steps in treating diabetic dyslipid-
emia should include optimization of glycemic control, dietary reinforcement, and a prescription of aerobic exercise. Strict dietary parameters for diabetic factors for coronary artery disease. Initial steps in treating diabetic dyslip-
emia should include optimization of glycemic control, dietary reinforcement, and a prescription of aerobic exercise. Strict dietary parameters for diabetic patients with dyslipidemia call for less than 35% of daily calories as fat, with less than 7% of total calories as saturated fat and less than 200 mg/day of dietary cholesterol (the NCEP Step II diet). Regular aerobic exercise will help by raising LDL levels, and weight loss achieved through exercise can further attenuate lipid abnormalities. Prospective trials using the fibrin acid derivative gemfibrozil to lower triglyceride levels and to raise HDL levels have produced improved cardiovascular outcomes (Veterans Affairs HDL Intervention Trial), although a subsequent study (FIELD) involving the derivative gemfibrozil to lower triglyceride levels and to raise HDL levels did not reduce the rate of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke compared with simvastatin alone in patients with type 2 diabetes.\footnote{Particularly given all these concerns, patients should have their statin titrated aggressively first before any consideration of combi-
nation therapy is made.}

Omega fatty acid fish oil supplements represent an additional option for patients with elevated triglycerides, particularly those with mild elevations in whom pharmacologic drug therapy may not be considered warranted. There are few data with these agents.

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\textbf{SUGGESTED READINGS}


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\textbf{ADDITIONAL SUGGESTED READINGS}


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