SUMMARY

Although type 1 and type 2 diabetes represent the vast majority of affected individuals with the disease, not all cases of diabetes fit neatly into these categories. A smaller in magnitude, but clinically significant, subset of patients may develop diabetes from a different pathophysiology. These forms may occur at any stage of life and be acquired environmentally, iatrogenically, as a result of a genetic mutation that predisposes to type 1, type 2, or a combined form of diabetes, or in other metabolic disorders where hyperglycemia is more likely to develop.

Congenital viral infections, predominantly rubella and cytomegalovirus (CMV), have historically been linked to diabetes. Although they are presently not observed often in the United States, rubella continues to represent a potential important etiology given fluctuation in vaccination rates. Multiple other viruses have been implicated as potential pathogens in triggering the autoimmune response or through direct infection of the pancreas.

Cystic fibrosis-related diabetes (CFRD) affects 12% of children with cystic fibrosis and 33% of adults with cystic fibrosis. CFRD is an important comorbidity to diagnose and treat, as patients with CFRD are at increased risk for mortality and treatment with insulin improves clinical outcomes.

Pancreatitis-related diabetes may account for 0.5%–1% of all new cases of diabetes in the general population. Some of these individuals will seek elective pancreatectomy due to persistence of pain associated with pancreatitis flares and poor quality of life. Islet autotransplantation continues to develop as a procedure to prevent diabetes in these patients.

Hemochromatosis, a disorder of iron metabolism, is present in 0.5%–1% of the population in the United States. Within this population, 7%–40% will eventually develop diabetes. These patients have evidence for both increased insulin resistance and insulin deficiency, which can lead to clinical diabetes.

Drugs associated with diabetes represent perhaps one of the most important other types of diabetes given the sheer numbers of pharmacologic agents implicated and the numbers of patients treated. Glucocorticoids are the most commonly encountered and most frequently identified agents that result in diabetes. In addition, other immunosuppressive agents used in transplant medicine, pharmacologic agents used in cardiovascular disease prevention, some antimicrobial and antiviral agents, hormone replacement therapies, and environmental pollutants have all been linked to development of diabetes.

Diabetes can also be part of an immune-mediated syndrome or underlying endocrinopathy. These forms may occur in disorders with a single gene defect (e.g., APS-1 or IPEX syndrome) and highlight the importance of screening for other endocrinopathies. Increased secretion of several hormones, including cortisol, growth hormone, thyroid hormone, aldosterone, epinephrine, and gut hormones, can also result in diabetes. Thus, patients with hypersecretion syndromes should be screened for diabetes as a comorbid condition.

Several relatively common genetic syndromes are associated with an increased risk for either type 1 or type 2 diabetes. Diabetes can be particularly challenging in populations with these syndromes, which are often associated with developmental delays, making prevention efforts paramount. Screening and treatment should be part of routine management in those syndromes where diabetes has been most strongly linked.

Other unique associations have emerged representing the last grouping of other diabetes forms. Diabetes occurs in up to 25% of transplant recipients. Risk is predominantly modified by the type of agent used posttransplant and inversely correlated with length of time from transplant. Infants with a history of intrauterine growth retardation are more likely to have characteristics of type 2 diabetes later in life, illustrating the importance of in utero nutrition and fetal programming. Similarly, children and adults with severe malnutrition may also develop diabetes that is distinct from other forms. Mutations in mitochondrial DNA can result in another form of maternally inherited diabetes, either as part of a distinct neurologic syndrome or on its own.

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Although type 1 and type 2 diabetes represent the vast majority of affected individuals with disease, not all cases of diabetes fit neatly into one of these two common categories. A smaller in magnitude, but clinically significant, subset of patients may develop diabetes stemming from a different pathophysiology. These forms may occur at any stage of life and be acquired environmentally, iatrogenically, as a result of a genetic mutation that predisposes to type 1, type 2, or a combined form of diabetes, or in other metabolic disorders where hyperglycemia is more likely to develop. This chapter describes the scenarios in which these less frequently encountered forms of diabetes may occur. It is important to remember that these forms of diabetes collectively represent a very small overall percentage of diabetes cases compared to type 1 and type 2 diabetes, yet they remain critically important representations of the expanding diabetes phenotype (Table 6.1). Chapter 1 Classification and Diagnosis of Diabetes summarizes all types of diabetes as classified by the American Diabetes Association (ADA); types of diabetes arising from single gene defects are described in Chapter 7 Monogenic Forms of Diabetes.

### TABLE 6.1. Summary of Other Types of Diabetes, Synopsis of Pathophysiology, and Prevalence

<table>
<thead>
<tr>
<th>TYPE OF DIABETES</th>
<th>PATHOPHYSIOLOGY</th>
<th>APPROXIMATE PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes due to infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital rubella</td>
<td>Debated—possible direct viral effect on beta cells and/or increased insulin resistance</td>
<td>Rare overall due to the MMR (Measles, Mumps, and Rubella) vaccine; 0%–25% of congenital rubella survivors</td>
</tr>
<tr>
<td>Congenital cytomegalovirus (CMV)</td>
<td>Weak link proposed—CMV can directly infect beta cells.</td>
<td>Case reports without clear linkage to diabetes</td>
</tr>
<tr>
<td>Other infections</td>
<td>Possible molecular mimicry</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cystic fibrosis-related diabetes (CFRD)</td>
<td>Reduced beta cell mass with insulin insufficiency, inflammation-related insulin resistance</td>
<td>15%–20% of adolescents with cystic fibrosis; prevalence increases with age.</td>
</tr>
<tr>
<td>Diabetes due to pancreatitis and total pancreatectomy</td>
<td>Insulin deficiency, pancreatic polypeptide deficiency, hepatic insulin resistance</td>
<td>Variable reports: 0.5%–1.15% of diabetes overall and up to 5%–10% of diabetes in select populations</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>Both insulin deficiency and insulin resistance have been implicated.</td>
<td>Variable reports: 7%–40% of patients with hemochromatosis</td>
</tr>
<tr>
<td>Drug and chemical-induced diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>Decreased hepatic and peripheral insulin sensitivity, enhancing glucose release</td>
<td>Related to glucocorticoid dose; 19%–25% of patients on glucocorticoids</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Unclear; impaired beta cell function, increased insulin resistance, and weight gain</td>
<td>Unknown</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Beta 2 blockade inhibits insulin secretion and may increase insulin resistance.</td>
<td>22% relative risk increase compared to other antihypertensive medications</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Likely related to the hypokalemic effect inhibiting insulin secretion</td>
<td>Dose-related; higher risk than with other diuretics</td>
</tr>
<tr>
<td>HMG Co-A reductase inhibitors</td>
<td>Unclear; decrease uptake of peripheral glucose</td>
<td>9% increased risk of diabetes compared to other cholesterol medications</td>
</tr>
<tr>
<td>Niacin</td>
<td>Unknown</td>
<td>37% relative risk increase of diabetes compared to placebo</td>
</tr>
<tr>
<td>HIV antiretroviral therapy</td>
<td>Unclear; may increase insulin resistance through inhibition of GLUT4 glucose transporter, through lipodystrophy, or through mitochondrial DNA damage</td>
<td>Related to duration of therapy</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Unknown</td>
<td>32% increased risk over other anti-Pneumocystis carinii pneumonia medications</td>
</tr>
<tr>
<td>Growth hormone (GH)</td>
<td>Insulin counterregulatory hormone; increases gluconeogenesis and decreases peripheral glucose uptake</td>
<td>Sixfold relative increased risk with GH therapy</td>
</tr>
<tr>
<td>Oral contraceptives and progestins</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Environmental toxins and pollutants (various)</td>
<td>Alterations in immune system function and glucose metabolism</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Table 6.1 continues on the next page.
### TABLE 6.1. (continued)

<table>
<thead>
<tr>
<th>TYPE OF DIABETES</th>
<th>PATHOPHYSIOLOGY</th>
<th>APPROXIMATE PREVALENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rare autoimmune forms of diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmune polyendocrine syndromes (APS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APS 1</td>
<td>Autoimmune type 1 diabetes</td>
<td>4%–18% of patients with APS-1 develop diabetes.</td>
</tr>
<tr>
<td>APS 2</td>
<td>Autoimmune type 1 diabetes</td>
<td>60% of patients with APS-2 develop diabetes.</td>
</tr>
<tr>
<td>IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked)</td>
<td>Autoimmune type 1 diabetes</td>
<td>Up to 60% of patients with IPEX develop diabetes.</td>
</tr>
<tr>
<td><strong>Rare forms of immune-mediated diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiff man syndrome</td>
<td>Neuroendocrine antibody-mediated islet destruction</td>
<td>33% of patients with Stiff man syndrome develop diabetes</td>
</tr>
<tr>
<td>Anti-insulin receptor antibodies</td>
<td>Antagonistic blocking of the insulin receptor</td>
<td>Very rare</td>
</tr>
<tr>
<td><strong>Endocrinopathies associated with diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acromegaly</td>
<td>GH is an insulin counterregulatory hormone; increases gluconeogenesis and decreases peripheral glucose uptake.</td>
<td>60% glucose intolerance; up to 56% of patients with acromegaly, which has a prevalence of 40 cases per 1 million people</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Glucocorticoids decrease hepatic and peripheral insulin sensitivity, enhancing glucose release.</td>
<td>40% of cases with Cushing syndrome</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>Alpha-2 adrenergic receptor stimulation decreases insulin sensitivity.</td>
<td>25%–75% of cases with pheochromocytoma have abnormal glucose tolerance.</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td>Elevated aldosterone levels contribute to insulin resistance.</td>
<td>25% of patients with primary hyperaldosteronism with normal glucose tolerance.</td>
</tr>
<tr>
<td>Thyroid dysfunction</td>
<td>Unclear; impaired insulin secretion and decreased peripheral insulin sensitivity</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tumors of endocrine pancreas or gut</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Insulin counterregulation, increased gluconeogenesis, and insulin resistance.</td>
<td>30%–90% of cases associated with diabetes</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Insulin counterregulation, increased gluconeogenesis, and insulin resistance.</td>
<td>Unknown</td>
</tr>
<tr>
<td>POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) syndrome</td>
<td>Unclear; increased levels of cytokines</td>
<td>Glucose intolerance or diabetes in 50% of patients with POEMS</td>
</tr>
<tr>
<td><strong>Congenital syndromes with long-term risk for diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Unclear; increased risk of both autoimmune processes and obesity and insulin resistance</td>
<td>Threefold to fourfold increased relative risk compared to general population</td>
</tr>
<tr>
<td>Bardet-Biedel syndrome</td>
<td>Unclear; increased obesity</td>
<td>Unknown</td>
</tr>
<tr>
<td>Alstrom syndrome</td>
<td>Unclear; increased insulin resistance and obesity</td>
<td>Up to 68% develop type 2 diabetes by late adolescence.</td>
</tr>
<tr>
<td>Prader-Willi syndrome (PWS)</td>
<td>Related to insulin resistance and obesity</td>
<td>7%–24% of patients with PWS</td>
</tr>
<tr>
<td>Turner Syndrome</td>
<td>Increased risk for autoimmune conditions and insulin resistance</td>
<td>Fourfold increased risk of type 1 diabetes; threefold to fourfold increased risk of type 2 diabetes</td>
</tr>
<tr>
<td>Williams syndrome</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Unique populations at risk for diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transplant recipients</td>
<td>Unclear and variable; increased insulin resistance and insulin deficiency; medication-related</td>
<td>2%–25% of posttransplant patients</td>
</tr>
<tr>
<td>Intrauterine growth retardation patients</td>
<td>Increased insulin resistance</td>
<td>47% increased risk of diabetes over the lifetime</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>Unclear</td>
<td>Very rare in the United States</td>
</tr>
<tr>
<td>Mitochondrial disorders</td>
<td>Impaired islet cell function</td>
<td>Up to 1% of diabetes patients</td>
</tr>
<tr>
<td>Type 1b diabetes</td>
<td>Unclear; insulin-deficiency, resulting in DKA</td>
<td>Increased risk in select ethnicities</td>
</tr>
</tbody>
</table>

Chapter 1 Classification and Diagnosis of Diabetes summarizes all types of diabetes as classified by the American Diabetes Association; types of diabetes arising from single gene defects are described in Chapter 7 Monogenic Forms of Diabetes. Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient. APS, autoimmune polyendocrine syndrome; CFRD, cystic fibrosis-related diabetes; CMV, cytomegalovirus; DKA, diabetic ketoacidosis; GH, growth hormone; GLUT, glucose transporter; HIV, human immunodeficiency virus; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome; PWS, Prader-Willi syndrome.

CONGENITAL VIRAL INFECTIONS

CONGENITAL VIRAL INFECTIONS AND DIABETES

Congenital viral infections may play a direct role in causing diabetes, at least in a small subset of patients. In utero exposures to rubella and, to a lesser extent, to cytomegalovirus (CMV) have been linked to subsequent development of diabetes. These cases are now extremely rare in the United States, related most notably to the MMR (Measles, Mumps, and Rubella) vaccine that has dramatically reduced the occurrence of congenital rubella in the Western world. The most recent estimates from the Centers for Disease Control and Prevention report an incidence of one congenital rubella infection case per year in the United States, with the majority of such cases occurring in children whose mothers were born outside the United States (1). Given the potential reemergence of viral disease in unvaccinated populations (2), congenital viral infections, rubella in particular, still represent an important form of diabetes to consider. Perhaps more importantly, a number of viruses, acquired outside the newborn period, have also been implicated in the pathophysiology of autoimmune, inflammatory forms of diabetes. Although the proposed mechanisms for this relationship are varied and not yet validated, viruses remain an important proposed etiology behind changes in incidence patterns in the United States and globally.

**Congenital Rubella**

The virus most strongly linked to diabetes is rubella. Congenital rubella infection, particularly when acquired during the first trimester, is a potentially lethal disease to the fetus. In those infants that survive, the congenital rubella syndrome (CRS) includes deafness, cataracts, and cardiac defects. A variety of other associations, some occurring later in childhood, have been described (3), including diabetes.

Estimates for the prevalence of diabetes among survivors of congenital rubella vary widely. Some studies report no increased risk of diabetes (4,5). In contrast, in Australia, 20%–22% of survivors of a 1940–1941 congenital rubella outbreak cohort developed diabetes compared to 13% of controls (6,7,8). In the United States, the 1962–1965 rubella epidemic resulted in a reported 20,000 cases of CRS (1). Of these survivors, 12% were reported to be either treated with insulin for a diagnosis of diabetes or to have abnormal oral glucose tolerance (9). In another U.S. cohort, 22% of congenitally infected individuals developed diabetes or glycemic abnormalities (10). Differences among these studies are likely related to the severity of individual CRS (11), as well as differences in case reporting and data collection.

The underlying pathophysiology for rubella-associated diabetes is still controversial. Reflecting this confusion, the International Society for Pediatric and Adolescent Diabetes categorizes diabetes associated with rubella as not specifically a form of type 1 or type 2 diabetes. Proposed mechanisms for diabetes related to rubella infection include both a direct viral effect on the beta cell and increased insulin resistance (4).

In vivo, the rubella virus has been shown to disrupt insulin secretion (12), and this may occur through multiple mechanisms. Direct infection and resulting insulin may occur in rubella and other viral infections (12,13,14,15), though this is not always observed. Autoimmune markers have been observed with an increased frequency in some (13), but not all studies (14). Therefore, predisposition to autoimmune diabetes following rubella may occur predominantly in those individuals already at an increased risk based on their human leukocyte antigen (HLA) haplotypes (9,15).

Increased insulin resistance and a clinical picture more like type 2 diabetes have also been described in survivors of congenital rubella infection. In the Australian cohort, diabetes did not develop for decades, and the majority of patients were treated with diet alone or oral medication (6,7,8). Hyperinsulinemia associated with abnormal glucose tolerance has been shown in nonobese subjects with a history of intrauterine rubella infection (9). Intrauterine growth restriction is frequently associated with congenital viral infection and is associated with insulin resistance later in life (16), potentially offering a mechanism by which congenital rubella infection might predispose affected individuals to insulin resistance and later risk for type 2 diabetes (see the section Intrauterine Growth Retardation).

Thus, data suggest some increased risk of diabetes following congenital rubella infection. This may be related to a combination of both direct viral-mediated in utero damage to beta cells and an element of postnatal insulin resistance related to intrauterine growth restriction. The diabetes phenotype of an individual may ultimately be dependent upon the severity of these insults, as well as genetic predisposition to additional risk factors for beta cell dysfunction and insulin resistance.

**Congenital Cytomegalovirus**

CMV is one of the most common perinatal viral pathogens worldwide. In the most severe cases, intrauterine CMV infection can result in fetal demise, and amongst survivors, 10%–15% develop hearing loss, cognitive delays, and significant neurologic impairment. Approximately eight out of every 1,000 infants born in the United States will be infected with CMV, and two of these infants (equal to 5,000 infants each year in the United States) will have permanent comorbidities related to their infection (17).

The link between congenital CMV infections and childhood diabetes is weak. It was first proposed following a case report of a child infected with CMV in utero who developed diabetes at age 13 months (18). Further evidence was provided by demonstrating that CMV can directly infect beta cells of infected infants (19), though subsequent in vitro experimentation did not show a deleterious effect on fetal beta cell function (20). To this point, epidemiologic data have not supported an association between CMV infection and later diabetes (21,22). Similar data have not yet been published in the United States, but registry efforts, such as the
Type 1 Diabetes Exchange (23) and the SEARCH for Diabetes in Youth study (24), may further clarify this issue.

OTHER INFECTIONS
Viral infections occurring after the newborn period have been postulated to play a role in the etiology of diabetes, though this remains a controversial area of study (25,26). Although not completely understood, the proposed viral-mediated mechanisms include the concepts of: molecular mimicry, where viral antigens such as those present on enteroviruses, are sufficiently similar to beta cell antigens to allow crossreactivity; gastrointestinal viral infections leading to changes in gut permeability and/or gastrointestinal flora; direct beta cell or nearby pancreatic tissue infection; or a general state of inflammation and immune activation, which “spills over” to the pancreas (27,28). These hypotheses suggest that in at-risk individuals, the immune system can be “fooled” by viruses into an inflammatory response against beta cells. Enteroviruses (i.e., Coxsackie virus B), rotovirus, CMV, and mumps exposures have all been associated with eventual onset of type 1 diabetes in this regard. A nonspecific viral-like illness is often observed prior to the onset of clinical disease, further complicating the etiologic picture. These clinical observations may represent the “stressful event” in individuals who already have underlying autoimmune insulinitis that leads to clinical presentation rather than a direct infection of the pancreas. This topic is discussed in further detail in Chapter 11 Risk Factors for Type 1 Diabetes.

CYSTIC FIBROSIS-RELATED DIABETES
Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in persons with cystic fibrosis (CF). It can occur at any age but is more common as patients get older. CFRD occurs equally between men and women and has been reported in <5% of children with CF age ≤10 years, 15%–20% of adolescents, 40% of those in their twenties and thirties, and approaching 50% of those age >40 years (Figure 6.1) (29). In CF centers across the United States, the median prevalence of CFRD is approximately 12% in individuals age <18 years and 33% in adults (30). Based on 2013 estimates from the Cystic Fibrosis Foundation patient registry, just over 28,000 individuals (50.3% children) have been diagnosed with CF in the United States, equating to an absolute number of 1,700 and 4,600 cases of CFRD in children and adults, respectively. In addition, 10%–30% of women with CF without CFRD develop gestational diabetes during pregnancy (31,32).

Risk of diabetes in CF is increased by the use of glucocorticoids or multiple other factors associated with worsening pulmonary disease (33). Lung transplant recipients, who use other immunosuppressives in CF, represent another high-risk group (34). There are important differences among CFRD, type 1 diabetes, and type 2 diabetes (Table 6.2), which necessitate a unique approach to diagnosis and management.

PATHOPHYSIOLOGY
Reduced beta cell mass leading to insulin insufficiency is present in essentially all CF patients. Several proposed mechanisms may account for the loss, including increased oxidative stress leading to beta cell injury, a dysfunctional CFTR protein, and collateral loss of islets as exocrine tissue is destroyed (35). Function of the remaining beta cells is influenced by genetic susceptibility (36) and, perhaps, the CF chloride channel defect itself (37). Variable insulin resistance-related inflammation and infection are not as important as insulin insufficiency in the pathogenesis of CFRD, but they assume a greater role during periods of stress, such as acute pulmonary infectious exacerbations.

DIAGNOSIS
The diagnostic criteria for CFRD were updated in 2010 in North America by the CFRD Guidelines Committee in a position statement cosponsored by the ADA and the Cystic Fibrosis Foundation and endorsed by the Pediatric Endocrine Society (38). The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates. During a period of stable baseline health, the diagnosis of CFRD can be made in CF patients according to standard ADA criteria. It should be noted, however, that low or normal glycosylated hemoglobin (A1c) levels do not exclude the diagnosis of CFRD, because A1c is often spuriously low in CF, perhaps due to more rapid red
TABLE 6.2. Characteristics of Type 1 Diabetes, Type 2 Diabetes, and Cystic Fibrosis-Related Diabetes

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>TYPE 1 DIABETES</th>
<th>TYPE 2 DIABETES</th>
<th>CYSTIC FIBROSIS-RELATED DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying pathophysiology</td>
<td>Insulin deficiency</td>
<td>Primarily insulin resistance with variable insulin insufficiency</td>
<td>Primarily insulin insufficiency, with features of insulin resistance</td>
</tr>
<tr>
<td>Exocrine deficiency</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Risk for ketoacidosis</td>
<td>Common</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Risk for microvascular</td>
<td>Common</td>
<td>Common</td>
<td>Common, but milder</td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin only</td>
<td>Diet, oral hypoglycemic agents, glucagon-like peptide-1 agonists, insulin</td>
<td>Insulin only</td>
</tr>
<tr>
<td>Dietary guidelines</td>
<td>Well-balanced diet, account for carbohydrate consumption</td>
<td>Lower calorie, balanced diet with limited carbohydrate consumption</td>
<td>High calorie, well-balanced diet, account for carbohydrate consumption</td>
</tr>
</tbody>
</table>


blood cell turnover. Diagnosis of gestational diabetes in a CF patient should be made based on the recommendations of the International Association of Diabetes and Pregnancy Study Groups (39). CF patients with gestational diabetes are not considered to have CFRD, but they require CFRD screening 6–12 weeks after the end of the pregnancy.

SCREENING
CFRD develops insidiously, so screening is important. The North American CFRD Guidelines Committee determined that the 2-hour 75 g (1.75 g/kg) oral glucose tolerance test (OGTT) is the screening test of choice for CFRD (38). Nearly two-thirds of patients with CFRD do not have fasting hyperglycemia (29). It is important to identify these individuals because they are at high risk for significant lung function decline (40) and because insulin therapy has been shown to improve nutritional status in this population (41).

Annual screening for CFRD should begin by age 10 years. During acute pulmonary exacerbations requiring intravenous antibiotics and/or systemic glucocorticoids, patients should be screened for CFRD by monitoring fasting and 2-hour post-prandial glucose levels for the first 48 hours. Screening for CFRD by measuring mid- and immediate post-feeding plasma glucose levels is recommended for CF patients on continuous enteral feedings. Women with CF who are planning a pregnancy should be screened for preexisting CFRD, and screening for gestational diabetes is recommended at both 12–16 weeks and 24–28 weeks gestation, using a 2-hour 75 g OGTT. There is emerging evidence that mid-OGTT glucose levels may be even more predictive of clinical decline than the 2-hour level, and thus, consideration should be given to measuring glucose levels every half-hour during the 2-hour test (42,43,44,45). The role of continuous glucose monitoring is not yet clear. Glycemic elevation can be detected by continuous glucose monitoring in patients with CF long before the OGTT diagnosis of diabetes, but the clinical significance of these brief elevations in glucose excursion remains unknown (42,46).

MANAGEMENT
Persons with CFRD should be treated by a multidisciplinary team with expertise in diabetes and CF and should receive ongoing diabetes self-management education. Insulin is the only recommended medical treatment (38). Insulin stabilizes lung function and improves nutritional status in patients with CFRD (29,41,47). Patients with CFRD should strive to attain plasma glucose goals per the ADA recommendations for all people with diabetes, bearing in mind that individualization is important and higher insulin doses are required during times of acute illness. Oral diabetes agents are not recommended outside the context of clinical research trials.

CFRD dietary recommendations are very different from those for people with type 1 or type 2 diabetes (Table 6.2). CF patients require a high-calorie, high-salt, high-fat diet. Caloric restriction is almost never appropriate. For patients on insulin therapy, carbohydrate counting is useful for determining the pre-meal insulin dose. Small, uncontrolled studies suggest that patients with impaired glucose tolerance might benefit from insulin therapy with weight gain and improvement in pulmonary function (47,48,49,50), but this has not yet been proven in controlled trials and, thus, is not standard of care (38).

COMPLICATIONS AND PROGNOSIS
Ketoacidosis is rare in CFRD because of the persistence of endogenous insulin and because glucagon levels are low. Severe hypoglycemia is not a common problem, but education about the symptoms, prevention, and treatment of hypoglycemia, including the use of glucagon, is recommended for patients with CFRD and their care partners. Diabetes microvascular complications occur in CFRD, but they are usually relatively mild in nature (51,52). Annual monitoring for diabetes microvascular complications is recommended using ADA guidelines, beginning 5 years after the diagnosis of CFRD or, if the exact time of diagnosis is not known, at the time that fasting hyperglycemia is first diagnosed. Blood pressure should be measured at every routine diabetes visit and hypertension treated per ADA guidelines (but without salt or protein restriction). Death from macrovascular complications has not been reported in CF.

Several studies showed an insidious decline in clinical status in the years before the diagnosis of CFRD, in the insulin-insufficient, prediabetic state (53,54,55,56,57,58). Following the recognition of diabetes as a potential comorbidity in the 1970s, increased mortality was
those without diabetes (53,59,60,61,62). Those with CFRD, like all CF patients, almost always die from pulmonary failure. Diabetes has been directly implicated in the pathophysiology of CF lung function decline because of both the catabolic effect of insulin insufficiency on nutritional status and muscle mass (63,64,65,66) and the negative impact of chronic hyperglycemia on lung function (43,67,68,69), the latter of which may create a proinflammatory, bacteria-permissive environment. The catabolic effect of insulin insufficiency may be most important in growing children (70,71,72). In 2009, routine screening and early institution of insulin therapy were shown to significantly reduce the excess mortality associated with diabetes in CF (29) and improve nutritional status even in patients very early in the course of diabetes with normal A1c and normal fasting glucose levels. Thus, while the risk of microvascular and macrovascular complications is not a compelling reason for early diagnosis and aggressive institution of insulin therapy in CF, the positive impact of insulin therapy on nutritional status, lung disease, and survival necessi-
tates that patients at a minimum achieve ADA goals. Ongoing studies are deter-
moving whether even more aggressive goals are appropriate in CF.

**DIABETES DUE TO PANCREATECTOMY**

**DESCRIPTION OF DIABETES DUE TO PANCREATECTOMY**

Diabetes due to disorders of the exocrine pancreas is characterized under other specific types of diabetes by the ADA (73). In 1980, the prevalence of diabetes due to pancreatitis was estimated at the relatively low rate of 0.5%–1.15% of all cases of diabetes in the United States and Western world (74,75). Data from select populations and other more recent studies from 2011, however, have indicated that the prevalence of pancreatogenic diabetes may be significantly higher, in the range of 5%–10% of all cases of diabetes (76,77). Chronic pancreatitis (CP) comprises approximately 75% of all other non-type 1 or type 2 cases of diabetes (78). Among patients with established CP, the prevalence of diabetes has been estimated at 26%–80% of patients, depending on duration and severity of disease (79). Advances in beta cell biology have elucidated newer etiologies of pancreatogenic diabetes as a pathologically distinct form of diabetes that to this point has been underrecognized (80,81).

**Pathophysiology**

Unlike the distinct mechanisms known to occur in the more common forms of type 1 or type 2 diabetes, diabetes associated with pancreatitis is characterized by a unique constellation of insulin deficiency, pancreatic polypeptide (PP) deficiency, and hepatic insulin resistance. PP is secreted predominantly by the F cells in islets at the head of the pancreas, and its prolonged absence promotes hepatic insulin resistance in human and animal studies (76). Patients whose pancreatic head has been lost or damaged due to trauma, complete or partial surgical removal, or chronic fibrosis are predisposed to PP deficiency and subsequent insulin resistance. Chronic inflammation, particularly in those who carry high-risk alleles for genes associated with inflammation, place the beta cell at risk for eventual damage, loss of insulin secretory capacity, and development of diabetes (79,82). In patients with pancreatitis, the inflammatory and destructive process, unlike that of type 1 diabetes, is not selective and also results in loss of glucagon-producing alpha cells and PP cells (79). In addition, in patients with CP, the intestinal glucoregulatory hormones of glucose-dependent insulinotropic peptide and glucagon-like peptide 1 have impaired production, secretion, and/or binding (76,83). Some studies have shown that these deficits are reversible with pancreatic enzyme replacement, suggesting that malabsorption also plays a role in the deficit of these hormones (83). Taken together, this complex mixture of islet cell destruction, insulin resistance, and coregulatory hormone dysfunction produces a complex endocrine phenotype and a form of diabetes that is distinct from other forms of diabetes.

**Diagnosis and Clinical Characteristics**

Diagnosis of diabetes in patients with CP follows standard ADA guidelines for the diagnosis of diabetes (73). While the underlying diagnosis of diabetes remains straightforward, the classification of this type of diabetes remains complex and controversial. Diagnostic criteria have been proposed but have not been formally adopted or accepted (79,84).

Despite the clinical similarities in insulin resistance, impaired counterregulatory hormone function results in pancreatitis-related diabetes being a more erratic form of diabetes, in which hyperglycemia and hypoglycemia fluctuate more readily and tight glycemic control is more challenging. In severe forms of pancreatogenic diabetes, hypoglycemia unawareness is more common, with a high risk of life-threatening hypoglycemia due to the absence of pancreatic alpha cells (glucagon secretion) (76). Despite this risk of severe hypoglycemia, patients with pancreatitis-related diabetes experience significant hyperglycemia and are at risk for microvascular complications, such as retinal and renal diseases, with rates approaching those seen in patients with type 1 diabetes (76,85).

Depending on the extent of hyperglycemia and insulin resistance, patients with pancreatitis-related diabetes require therapy with an oral medication, such as the sensitizing agent metformin, and/or multiple daily injection therapy with long-acting and rapid-acting insulin analogues in a basal bolus fashion. Other medications used to treat type 2 diabetes can be considered, though few studies have been conducted to guide selection of one agent or class of agents over another. The conventional approach for oral agents favors metformin due to its well-established added benefit of decreasing the risk of pancreatic cancer (79,86,87,88,89), a known risk in this...
group. Other oral agents should be used with caution given the increased risk of osteoporosis (79) associated with thiazolidinediones and uncertain long-term outcomes with sulfonylureas (76). Incretin-based therapies are not well studied and should be used cautiously given the association with pancreatitis (79).

HEREDITARY/GENETIC PANCREATITIS

In addition to risk for development of diabetes, patients with CP often experience debilitating pain, narcotic dependence, and diminished quality of life. Increasingly, patients with CP are found to have an underlying genetic cause for their disease, resulting in classification of their pancreatitis as hereditary/genetic pancreatitis (HGP). The most common mutation associated with CP is a mutation of the cationic trypsinogen gene (protease, serine 1 or PRSS1). This mutation may account for up to 80% of patients with symptomatic HGP. All patients with CP are at significantly increased risk of developing pancreatic ductal adenocarcinoma (90,91,92). First symptoms of HGP typically present in childhood with pancreatic pain progressing to acute pancreatitis and eventually CP by the third decade of life (93). Patients afflicted with CP may seek total pancreatectomy (TP) for removal of the tissue associated with the pain and carcinoma risk (94). This procedure, when paired with islet autotransplantation (IAT), offers the benefit of pain control, reduced cancer risk, and the potential for preserved glycemic control.

The surgical approach of pancreatectomy with isolation, purification, and infusion of the patient’s islets has been well described (93,95,96,97,98,99,100). During the period of islet engraftment, the islets are particularly vulnerable to overstimulation by hyperglycemia in an anoxic environment, which contributes to beta cell loss (100,101,102). Thus, for the immediate posttransplant period, narrow-range glycemic control with a target blood glucose of 70–140 mg/dL (3.89–7.77 mmol/L) is essential for optimal islet engraftment and survival (100,103).

Cohort studies of patients have shown that following TPIAT, 80%–99% of patients denied the presence of pancreatitis pain and >80% denied the presence of any pain (93,95). Significant improvements across all quality-of-life measures have been observed after TPIAT procedure, with >85% of patients indicating that their health improved in the year after TPIAT (95).

Success of TPIAT, however, is most often correlated with long-term insulin independence. Although no single factor is predictive of insulin independence after TPIAT, the number of islet equivalents transplanted is the greatest predictor of long-term insulin independence with 2,000–5,000 IEq/kg often considered the threshold for improved outcomes (104). Prior pancreatic surgery is an important factor negatively impacting islet yield and insulin independence (104). After TPIAT, most patients have decreasing insulin demands for the first 3–12 months as islets engraft and insulin production improves. By 2 years posttransplant, approximately one-third of patients are insulin-independent, one-third require only minimal insulin therapy (once daily basal insulin), and one-third are insulin-dependent in a manner similar to type 1 diabetes patients undergoing islet allotransplantation (Figure 6.2) (93,95). In the period between 1 and 5 years posttransplant, approximately 10% of TPIAT patients go from insulin-independent to minimal insulin use, though at least 20% of patients are insulin-independent >10 years posttransplant (93,95).

PANCREATIC CANCER

Diabetes has been identified both as a risk factor for the development of pancreatic cancer and as a comorbidity subsequent to cancer diagnosis. An approximately twofold increased risk for pancreatic cancer exists for individuals with previously diagnosed diabetes (105,106,107). This risk appears to be greatest in older individuals with a more recent diagnosis of diabetes (108). Similarly, the cumulative

**FIGURE 6.2.** Islet Transplantation Rates of Success in Hereditary and Non-Hereditary Pancreatitis, 1977–2012

![Figure 6.2](image-url)

SOURCE: Reference 93, copyright © 2014 American College of Surgeons, reprinted with permission
risk of pancreatic cancer in subjects with CP is approximately 2% at 10 years of disease and 4% at 20 years of disease (109). Diabetes associated with pancreatitis has been shown to be an additional risk factor for development of pancreatic cancer (110). Conversely, in patients with a known gene mutation resulting in development of pancreatic cancer, approximately 80% of these patients will go on to develop concomitant diabetes (111).

HEMOCHROMATOSIS

Hemochromatosis is primarily an autosomal recessively inherited disease caused by mutations in the gene HFE and characterized by the clinical triad of bronzed skin, cirrhosis, and glycosuria. These clinical features result from the abnormal accumulation of excess iron deposition into various organs and tissues. Patients with hemochromatosis carry an increased mortality rate compared to the general population, particularly those with cirrhosis or diabetes (Figure 6.3) (112).

Four specific types of hemochromatosis have been described (Table 6.3) (113), though two primary mutations in HFE account for the majority of disease in patients. Prevalence of hemochromatosis varies widely in the general population depending on ethnic background. The highest prevalence occurs in individuals of Northern European ancestry. A study of non-Hispanic Caucasians in the United States showed a 9% heterozygous carrier rate for the most common disease-causing mutation in HFE, with an additional 0.5% of the population having homozygous mutation (114).

The prevalence estimates for diabetes in hemochromatosis patients range from 7% to 40% (115,116). However, a combined rate of 50% for diabetes and impaired glucose tolerance has been found after screening large clinic populations, a rate that was significantly higher than familial controls (117). Large variation in penetrance of disease among individuals with known mutations and phenotypic variations in expression of disease comorbidities, including diabetes, are probable factors contributing to the large variability in prevalence estimates (118). Additionally, earlier genetic diagnosis and presumed therapy may have impacted the prevalence rates of diabetes within the hemochromatosis population (119). In addition to individuals with hemochromatosis, excessive administration of iron in the form of oral supplements or repeated blood transfusions without adequate chelation can result in significant increases in iron stores and affect glucose tolerance. This is particularly true of individuals with hemoglobinopathies, bone marrow failure, or bone marrow transplant recipients where repeated

<table>
<thead>
<tr>
<th>FIGURE 6.3. Hemochromatosis: Long-Term Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="%7B%7D" alt="Graph showing cumulative survival in 163 patients with hemochromatosis compared with the normal population; in the same patients with (n=112) or without (n=51) cirrhosis; with (n=89) or without (n=74) diabetes; and in those depleted (n=77) or not depleted (n=75) of iron during the first 18 months of venesection. All differences were statistically significant (p&lt;0.05 to &lt;0.002 by log-rank test). SOURCE: Reference 112, copyright © 1985 Massachusetts Medical Society, reprinted with permission" /></td>
</tr>
</tbody>
</table>
red blood cell transfusions are common. Estimates for prevalence of iron overload among adult patients with sickle cell disease or thalassemia requiring repeated transfusion and in patients who have undergone stem cell transplantation are 9.7% (120) and 23% (121), respectively. Up to 32% of patients undergoing hematopoietic stem cell transplantation requiring repeated transfusion meet criteria for iron overload (122).

Both insulin deficiency and insulin resistance (123,124) have been implicated in the pathophysiology of diabetes in hemochromatosis. Knockout HFE mice develop increased islet iron deposits, increased markers of oxidative stress, and increased rates of apoptosis leading to decreased insulin secretory capacity when fed a diet high in iron (125). Insulin clamp studies also support a primary insulin secretory defect as the main factor responsible for progression to glucose intolerance (117). Increased body mass index (BMI, kg/m²) also seems to be associated with progression to diabetes, so some effect of insulin resistance cannot be discounted. However, studies of hemochromatosis patients with normal glucose tolerance demonstrate no difference in measures of insulin resistance (and insulin secretion) compared to matched, healthy controls (117). The severity of hepatic disease (presence of cirrhosis or fibrosis) appears to correlate with the prevalence of diabetes (117), though this has not been found in all cohorts (119). Thus, definitive conclusions regarding a central defect to this point are limited by small numbers, the confounder effect of insulin secretory capacity (126). In those individuals in whom diabetes has been diagnosed, exogenous insulin therapy should be provided for management. Lowering iron levels through phlebotomy can improve insulin sensitivity and secretion in patients with prediabetes but may be less efficacious in those with more advanced disease (118,130). Phlebotomy and subsequent iron depletion are associated with improved survival rates (Figure 6.3) (112).

### Drug and Chemical-Induced Diabetes

Multiple classes of pharmaceuticals have been associated with dysglycemia and progression to diabetes. Identifying the impact of specific drug classes can be challenging, since the disease processes they target are often independently associated with diabetes. In addition, treatment of some disorders requires a polypharmacy approach, making it difficult to isolate effects of one drug from another. For example, although hypertension itself is associated with an increased risk of diabetes (131), some drugs used to treat hypertension are independently associated with hyperglycemia (thiazides and beta blockers), while others are not (calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers). Thus, in most instances, causality cannot be proven conclusively between exposure to a medication and the occurrence of diabetes, and most reports do not fulfill rigorous criteria (Bradford-Hill) for cause-effect relationships. Moreover, additional confounders within this population (e.g., presence of a family history of diabetes) may also play a significant role in any relationship. A synopsis of the drugs most commonly associated with hyperglycemia or diabetes and their proposed mechanisms is provided in Table 6.4.
TABLE 6.4. Summary of Drugs Associated With Diabetes

<table>
<thead>
<tr>
<th>DRUG CLASS</th>
<th>SPECIFIC AGENTS</th>
<th>PROPOSED MECHANISM</th>
<th>PARTICULAR POPULATIONS AFFECTED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucocorticoids</td>
<td>More potent (dexamethasone, methylprednisolone)</td>
<td>Mechanism unknown</td>
<td>Transplant recipients</td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>Tacrolimus, cyclosporine &gt; sirolimus</td>
<td>Inhibit beta cell growth and function</td>
<td>Transplant recipients</td>
</tr>
<tr>
<td>Atypical antipsychotics</td>
<td>Clozapine, olanzapine, risperidone</td>
<td>Mechanism unknown</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>Non-selective beta blockers (e.g., propranolol)</td>
<td>Impair insulin release, increase insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Hydrochlorothiazide (HCTZ), diazoxide</td>
<td>Inhibit beta cell release</td>
<td>Dose-dependent</td>
</tr>
<tr>
<td>HMG Co-A reductase inhibitors</td>
<td>Atorvastatin, rosuvastatin, simvastatin</td>
<td>Increasing calcium influx and decreasing GLUT4 glucose uptake</td>
<td>Dose-dependent</td>
</tr>
<tr>
<td>Niacin</td>
<td>Niacin</td>
<td>§ insulin resistance</td>
<td></td>
</tr>
<tr>
<td>HIV antiretroviral therapy</td>
<td>Protease inhibitors (PI) (indinavir, saquinavir, ritonavir, nelfinavir) and nucleoside reverse transcriptase inhibitors (NNTI) ( stavudine, zidovudine, didanosine)</td>
<td>PI: increased insulin resistance through blockade of GLUT4 transportation. NNTI: increased insulin resistance, perhaps through induction of lipatrophy.</td>
<td>Patients with HIV—increased risk with higher BMI, older age, lipodystrophy</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Parenteral greater effect versus aerosolized</td>
<td>Beta cell toxicity</td>
<td>AIDS population, renal impairment</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Multiple formulations</td>
<td>Increased insulin resistance</td>
<td>Growth hormone-deficient children and adults, ± Turner syndrome</td>
</tr>
</tbody>
</table>

Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient. AIDS, acquired immune deficiency syndrome; BMI, body mass index; GLUT, glucose transporter; HIV, human immunodeficiency virus; NNTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitors.


**GLUCOCORTICOIDS**

Due to their potent immunosuppressive effect, glucocorticoids are used in a wide range of clinical entities. Glucocorticoids can affect glucose metabolism through multiple pathways. Their primary effect is via decreases in hepatic and peripheral insulin sensitivity, thereby enhancing hepatic glucose release and limiting uptake and transport of glucose in muscle and fat. Between 40% and 60% of all new endocrinology inpatient consultations are for glucocorticoid-related hyperglycemia (132). The overall odds ratio for development of diabetes in individuals taking glucocorticoids is approximately 1.36–2.31 (133). In adults with a history for malignancy or undergoing bone marrow transplantation, 19% experience glucose levels in a diabetes range (134), while 25% of kidney transplant recipients on glucocorticoid therapy develop hyperglycemia (135). The more potent glucocorticoids (dexamethasone, methylprednisolone), overall dose equivalent, and longer duration of treatment impart greater risk for development of diabetes (136,137). Risk for progression to diabetes is also modified by age, BMI, and ethnic background (138). Although a family history for type 2 diabetes may also impart risk (139), this has not been demonstrated in all studies (140). Excess glucocorticoids resulting in Cushing syndrome is reviewed in the section Endocrinopathies Associated With Diabetes.

**CALCINEURIN INHIBITORS**

The three primary calcineurin inhibitors—cyclosporine, sirolimus, and tacrolimus—have all been associated with diabetes. These drugs are used in transplant medicine as immunosuppressive agents to prevent graft rejection. A greater incidence of posttransplant diabetes has been noted for both cyclosporine and tacrolimus compared to sirolimus. See the section Transplant Recipients for additional discussion.

**ATYPICAL ANTIPSYCHOTICS**

Although schizophrenia itself is associated with an increased risk of diabetes, medications used to treat psychosis have a longstanding history of imparting risk as well. Second-generation antipsychotics, known as atypical antipsychotics, have been heralded for their effective treatment of psychotic disorders, while minimizing extrapyramidal side effects. However, there is a twofold greater increase in weight gain, hyperglycemia, and dyslipidemia in patients treated with this class of drugs (141). Several drugs within this class, including clozapine, olanzapine, risperidone, and quetiapine, have all been linked to weight gain and hyperglycemia. Other reports have reviewed each individual drug profile and their relative risks for diabetes (142). The drugs with the greatest consistent risk for diabetes are clozapine and olanzapine, while risperidone carries less risk. Although each of these drugs is associated with individual risks for weight gain (Figure 6.4) (143), the effect on blood glucose levels appears to be independent of weight. The etiology behind this effect on beta cell function and/or insulin resistance is not well understood.

**BETA BLOCKERS**

The risk for incident diabetes in patients on beta blockers is increased compared to other antihypertensive agents (other than thiazide diuretics) (144). A 22% increased risk for new diabetes in patients treated with beta blockers compared to other antihypertensives was identified in a meta-analysis of 94,492 patients (145).
Nonselective beta blockers (e.g., propranolol) appear to cause this hyperglycemic effect through their nonselective beta blockade of the beta 2 adrenoreceptor. Beta 1-selective blockers do not impart the same effect. An analysis from the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study showed no increase in diabetes among patients started on beta blockers. This apparent change in association may be related to the more current use of selective beta 1 receptor blockers (146). Thus, through the blockade of beta 2 receptors, beta blockers can inhibit insulin secretion but also may have an effect on raising insulin resistance (147).

THIAZIDE
Thiazides are commonly used for control of blood pressure and as a mild diuretic. The association between thiazide diuretics and hyperglycemia has been observed for over 50 years (148). In a meta-analysis of over 143,000 patients, incident diabetes was more likely to occur with the use of thiazide diuretics than any other antihypertensive agent (144). Hyperglycemia likely stems from the hypokalemic effect of thiazide diuretics (149). Hypokalemia inhibits the secretion of insulin and increases insulin resistance (150). Lower doses of thiazides do not impart the same risk for hyperglycemia (151). Similarly, diazoxide, which has avid binding affinity for the sulfonylurea receptor, inhibits insulin release and, thus, is frequently used in infants with congenital hyperinsulinism. Higher doses can result in excessive insulin inhibition and subsequent hyperglycemia.

HMG CO-A REDUCTASE INHIBITORS
Statins, widely heralded for their primary effect of reducing low-density lipoprotein (LDL) cholesterol and improving outcomes among individuals with heart disease, have had inconsistent associations with elevated glucose levels (152,153). However, there is growing evidence of a modest, yet potentially important relationship. A meta-analysis suggested a modest 9% increase risk for incident diabetes among statin users, equivalent to an overall increase of one case of diabetes for every 255 treated patients over a 4-year span (154). Furthermore, a Dutch study of type 2 diabetes patients found an increase in A1c of 0.3% in those treated with either atorvastatin or rosvastatin (155). The more potent statins (atorvastatin, simvastatin) and more intensive regimens appear to be associated with greater risk compared to less potent agents and regimens (156). Although causality has not been clearly established, statins appear to decrease the uptake of peripheral glucose through their effect on cholesterol content of glucose transporters (GLUT) (157). In 2012, the U.S. Food and Drug Administration (FDA) required a change to the safety label for all statin classes of medications, warning about the potential risk for increased glycated hemoglobin and fasting blood glucose levels. The proven benefits of cardiovascular risk reduction with statins probably still outweigh any potential for the effect of this drug class on glucose control.

NIACIN
Niacin is used in the treatment of hypertriglyceridemia and to assist in raising high-density lipoprotein (HDL) levels. In the Coronary Drug Project, in which men with a history of myocardial infarction were treated with niacin as an arm of therapy, a significant 37% increased risk in new cases of diabetes was found compared to placebo (158). Long-term treatment with niacin results in small but significant increases in fasting glucose levels (158,159). Among patients with preexisting diabetes taking niacin, a small but significant increase in A1c levels (0.3%) may occur (160). Similar effects of increased fasting glucose and insulin levels have been found in postmenopausal women treated with niacin (161).

HIV ANTIRETROVIRAL THERAPY
A warning by the FDA regarding the class of medications known as protease inhibitors and risk of hyperglycemia was first issued in 1997. Preceding this warning were numerous reports of hyperglycemia occurring in patients taking this newly established class of agents used in the treatment of HIV-positive patients. Although individuals with HIV do not appear to be at an overall increased risk for development of diabetes, the duration of antiretroviral therapy imparts significant risk (162,163). Risk in this population is also correlated with age, BMI, and presence of lipodystrophy. HIV-related lipodystrophy carries several features of the metabolic syndrome (Table 6.5) (164) and is known to associate with cardiovascular disease risk and type 2 diabetes. Among the group of nucleoside reverse transcriptase inhibitors, stavudine imparts the greatest risk for development
of diabetes, where each year of its use is associated with a 19% increase after adjustment for risk factors and lipids (165). This class of drugs may increase insulin resistance directly through inhibition of GLUT4 glucose transport or indirectly through induction of lipodystrophy or damage to mitochondrial DNA.

### PENTAMIDINE

Pentamidine is used in the prevention of *Pneumocystis carinii* infection in immunocompromised patients. Its use has been linked to hypoglycemia in the acute phase of treatment. However, hyperglycemia and even diabetic ketosis have been described during chronic therapy among AIDS patients (166, 167). Compared to an alternate treatment, parenteral pentamidine resulted in a significantly higher percentage of patients experiencing dysglycemia, including 32% who developed diabetes (168). Greater risk occurs in patients treated with higher doses and in those with underlying renal impairment. A similar, but less severe, effect may be observed using aerosolized pentamidine (169).

### GROWTH HORMONE

Growth hormone (GH), a counterregulatory hormone with antagonistic effect to insulin, increases gluconeogenesis and decreases peripheral glucose uptake (increased insulin resistance). In both GH-deficient patients (170) and those with acromegaly (171), there have been increased rates of diabetes (see the section Acromegaly). The availability of recombinant human GH in the early 1990s prompted concerns about the potential for GH-related deleterious metabolic effects.

A 2000 report found an increased rate of type 2 diabetes among children treated with GH therapy (172). This was confirmed in a subsequent analysis from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS), a multinational observational study of children treated with GH, compared to a reference cohort of age-matched children enrolled in the SEARCH for Diabetes in Youth study, a multicenter epidemiologic study conducted in six U.S. centers (173). In this study, among 5,591 patients in the United States treated with GH, five new cases of type 2 diabetes were identified versus an expected number of 0.59 cases (equivalent to a significant standardized incidence ratio of 8.5). This increase was observed exclusively in children with a diagnosis of GH deficiency versus other diagnoses. Among all children in this GH registry (international), an increase was also observed in girls with Turner syndrome. In an international database of GH-deficient adults started on GH, a sixfold increase in the observed versus expected cases of type 2 diabetes was found (174). There was no impact of GH dose or insulin-like growth factor 1 (an indirect marker of GH therapy) on diabetes risk. Greater risk was observed in those patients who were older or had higher BMI, higher blood pressure, and higher triglycerides, indicating that traditional risk factors still modify degree of risk in this population. Among adults on GH therapy, when an approach of individualized dosing using appropriate titration for clinical effect rather than a strict weight-based approach was used, no increase in hyperglycemia was typically observed (175).

Mechanistically, the potential impact of GH on diabetes risk occurs through alterations in insulin resistance, as demonstrated in studies of children with idiopathic short stature or born small for gestational age (176, 177). To this point, no effects on increasing glucose levels or new cases of diabetes have been identified in any study of children treated for idiopathic short stature (178).

### ORAL CONTRACEPTIVES AND PROGESTINS

Subtle changes to carbohydrate metabolism can occur in women using combined estrogen/progestin oral contraceptive pills. Modest increases in rates of impaired glucose tolerance, fasting glucose, and insulin have been identified in oral contraceptive users (179, 180). This effect appears to be predominantly related to the progestosterone, rather than the estrogen, component. In a 2012 report, approximately 10.6 million women in the United States used an oral contraceptive pill (181). Despite this potential risk, a link between clinical diabetes and oral contraceptive use has been inconsistent at best, perhaps in part related to the difficulty involved in controlling for other variables and confounders. No increase in cases of diabetes were identified in two prospective studies using estrogen/progestosterone combinations (182, 183). Moreover, glycemic control does not deteriorate among women with previously diagnosed diabetes taking an oral contraceptive (184).

### ENVIRONMENTAL TOXINS AND POLLUTANTS

Environmental toxins and triggers encompass a wide array of naturally occurring pathogens (e.g., viruses; see the section Congenital Viral Infections) and man-made toxins, contaminants, and pollutants that...
potentially could lead to or accelerate the development of type 1 or type 2 diabetes. Repeated exposures of the immune system to harmful chemicals or pollutants may trigger a type 1 diabetes autoimmune response or have a direct toxic effect on beta cells (185). Similarly, an association between exposure to air pollutants and development of type 2 diabetes has been proposed (186).

**RARE AUTOIMMUNE FORMS OF DIABETES**

**AUTOIMMUNE POLYENDOCRINE SYNDROMES**

Autoimmune type 1 diabetes is frequently observed as part of a constellation of other endocrine and non-endocrine autoimmune diseases termed autoimmune polyendocrine syndromes (APS) (187). APS can be further subdivided into two primary entities, APS-1 and APS-2, with some distinct and some overlapping clinical features (Table 6.6) (188). The incidence of APS-1 within the general population is exceedingly rare, approximating 1 new case for every 100,000 individuals, with highest prevalence rates in consanguineous and small founder populations (189). APS-2 is more common, with an estimated prevalence of 1 in 20,000 in the general population (190). Type 1 diabetes has been reported to occur in up to 20% of some populations with APS-1, but the rate more likely approximates 4%–18% (188). Type 1 diabetes is far more common in APS-2, occurring in up to 60% of patients and as the first manifestation in the majority of patients (189).

APS-1 is characterized phenotypically by the presence of mucocutaneous candidiasis, hypoparathyroidism, and/or adrenal insufficiency, though several other endocrine and systemic features have been observed less often (Table 6.6) (188). APS-1 is inherited in an autosomal recessive fashion, linked to mutations in the autoimmune regulator gene (AIRE) on chromosome 21 (191).

APS-2 forms the foundation for screening for other autoimmune conditions in the presence of type 1 diabetes. APS-2 is strongly associated with HLA haplotypes DR3/DQ2 and DR4/DQ8 (192,193,194). Patients with type 1 diabetes (particularly those with known high-risk HLA haplotypes) warrant screening for other autoimmune endocrinopathies, most notably autoimmune thyroiditis, Addison’s disease (autoimmune adrenalitis), celiac disease, and autoimmune hepatitis (188). Several other features of APS-2 have been described (Table 6.6).

**IMMUNODYSREGULATION POLYENDOCRINOPATHY ENTEROPATHY X-LINKED**

Immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome is a rare X-linked condition caused by mutations of the FOXP3 gene located on chromosome Xp11.3-q13.3 (195). This mutation results in a loss of the functional CD4+CD25+ T regulatory cells, which are essential to the prevention of autoimmunity (196,197,198). Patients with IPEX have a phenotype consisting of immunodeficiency, polyendocrinopathy, and enteropathy. IPEX is exceedingly rare with fewer than 150 affected individuals reported in 2011. Type 1 diabetes is frequently seen as part of the IPEX syndrome, with up to 60% of reported subjects affected, most commonly within the first year of life (195,199). Islet-specific antibodies (e.g., islet cell antibodies, glutamic acid decarboxylase [GAD] antibodies) are common in patients with IPEX (195). Patients typically present early in life with a triad of autoimmune enteropathy, autoimmune endocrinopathy, eczematous dermatitis, and immune dysfunction (196,200).

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**TABLE 6.6. Features of Autoimmune Polyendocrine Syndromes Types 1 and 2**

<table>
<thead>
<tr>
<th>TYPE 1</th>
<th>TYPE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addison’s disease*</td>
<td>Addison’s disease*</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Alopecia</td>
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<tr>
<td>Myasthenia gravis</td>
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<td>Asplenia</td>
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<td>Autoimmune bronchiolitis</td>
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<tr>
<td>Autoimmune thyroiditis</td>
<td>Autoimmune thyroiditis*</td>
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<tr>
<td>Chronic active hepatitis</td>
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<tr>
<td>Chronic candidiasis*</td>
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<tr>
<td>Dental enamel and nail dystrophy</td>
<td>Idiopathic heart block</td>
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<td>Ectodermal dysplasia</td>
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<td>Hypogonadism</td>
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<td>IgA deficiency</td>
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</tr>
<tr>
<td>Malabsorption syndrome</td>
<td>Celiac disease, dermatitis herpetiformis</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Pernicious anemia</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>Idiopathic thrombocytopenia</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td></td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>Type 1 diabetes*</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Vitiligo</td>
</tr>
</tbody>
</table>

* Primary hallmarks of disease

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Acromegaly has an estimated prevalence including Stiff man syndrome and anti-insulin receptor antibodies.

Stiff man syndrome is an organ-specific autoimmune disorder in which patients are frequently seropositive for a neuroendocrine antibody against the GAD 65 kD isoform (201). In addition to characteristic neurologic findings (chronic fluctuation of truncal and limb muscle rigidity and spasms), approximately 33% of patients with Stiff man syndrome develop diabetes, with approximately 43% of GAD-seropositive patients developing diabetes (201).

Another uncommon immune-mediated form of diabetes involves the formation of anti-insulin receptor antibodies, a process termed type B insulin resistance syndrome. Anti-insulin receptor antibodies may exhibit agonistic or antagonistic actions on the insulin receptor resulting in hypo- or hyperglycemia. Antagonistic antibodies have been documented in patients with systemic lupus erythematosus and other autoimmune conditions (73,202,203). Presence of the antagonistic anti-insulin receptor antibodies can cause severe hyperglycemia that is refractory to even very large doses of insulin (202).

ENDOCRINOPATHIES ASSOCIATED WITH DIABETES

ACROMEGALY
Acromegaly has an estimated prevalence of 40 cases per million people and is most often caused by a benign pituitary adenoma over-secreting GH (see the section Drug and Chemical-Induced Diabetes) (171). Glucose intolerance is extremely common in acromegaly, affecting >60% of patients (204). The prevalence of diabetes in acromegaly has been estimated in different series between 19% and 56% of patients (171). Higher GH levels, older age, and longer disease duration are significant predictors of development of diabetes within this population (205). Successful treatment of acromegaly with normalization in GH and insulin-like growth factor 1 improves glucose and insulin levels in patients with glucose intolerance; however, the improvement in symptoms of those who develop overt diabetes has been more limited (206,207,208).

CUSHING SYNDROME
Cushing syndrome is caused by chronic exposure to excessive glucocorticoids, either exogenously or endogenously (208). Glucocorticoids are the principal antagonistic hormones to insulin, and prolonged exposure to excess levels of these hormones can result in diabetes (see the section Drug and Chemical-Induced Diabetes). Glucocorticoids act on pancreatic beta cells to reduce insulin sensitivity and impair beta cell function (209,210). Diabetes due to chronic exposure to glucocorticoids plays an important role in the increased morbidity and mortality associated with Cushing syndrome (210,211). In patients with endogenous Cushing syndrome, impaired glucose tolerance occurs in approximately 50% of cases, and diabetes develops in approximately two-thirds of those cases (overall rate of 40%) (210). Longer duration and higher doses of glucocorticoids, presence of abdominal obesity, and family history of diabetes increase the risk for developing glucose intolerance and diabetes in patients with Cushing syndrome (138,212,213,214,215).

PHEOCHROMOCYTOMA
Pheochromocytomas are rare endocrine tumors that produce excessive catecholamines. Catecholamines act via alpha-2 adrenergic receptors to inhibit insulin secretion and beta adrenergic receptors to decrease insulin sensitivity (208,216). Glucose intolerance is seen in 25%–75% of patients with pheochromocytoma (216,217,218). Some small series have found diabetes prevalence rates up to 35% (208,216,219). Use of alpha-blocking agents improves insulin secretion and glucose tolerance, and surgical removal of the tumor improves insulin resistance (216,218,220).

PRIMARY HYPERALDOSTERONISM
Primary hyperaldosteronism is associated with glucose intolerance in about 25% of patients (221). From 2000 to 2010, understanding of the role of the renin-angiotensin-aldosterone axis in insulin resistance has undergone a paradigm shift. It was previously thought that aldosterone excess produced potassium depletion, which blunted insulin secretion. More recent research has shown that elevated plasma aldosterone levels directly contribute to insulin resistance (222). Aldosterone can impair insulin signaling in cardiovascular and renal tissue, fat, skeletal muscle, and in the liver (222).

THYROID DYSFUNCTION
Glucose intolerance is common in hyperthyroidism, though the mechanism for hyperthyroxinemia on dysglycemia remains unclear. Diabetes diagnosed by OGTT was identified in 11% of newly diagnosed Graves’ disease patients (223). Both impaired insulin secretion and decreased peripheral insulin sensitivity contribute to this association (224). Hyperthyroidism may worsen glucose intolerance through increased hexose intestinal absorption, decreased responsiveness to insulin, and increased glucose production (208). Increased insulin resistance also occurs in subclinical or frank hypothyroidism (225).

TUMORS OF ENDOCRINE PANCREAS OR GUT
Glucagonoma and somatostatinoma are tumors that produce glucagon and somatostatin, respectively. The overproduction of hormones in these rare tumors often leads to glucose intolerance or overt diabetes as these hormones are potent insulin counterregulatory agents (208). The incidence of both glucagonomas and somatostatinomas
are exceedingly rare at 0.1–1 case per 1,000,000 individuals. Patients with somatostatinomas arising from the pancreatic head rather than duodenum (50%–66% of all patients), typically have classic triad of diabetes, steatorrhea, and cholelithiasis (226). Diabetes occurs in 30%–90% of patients with glucagonomas (also characterized by rash) (227,228).

Surgical resection of the tumor and any metastases is the preferred therapy for both conditions (228).

POEMS SYNDROME
POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is a rare paraneoplastic syndrome due to an underlying plasma cell disorder. Detailed understanding of the pathogenesis is lacking, though increased levels of cytokines, particularly vascular endothelial growth factor, are common in the disorder (229). Endocrinopathy is a major feature of POEMS syndrome, with glucose intolerance or diabetes occurring in approximately half of cases (229).

CONGENITAL SYNDROMES WITH LONG-TERM RISK FOR DIABETES

A large number of congenital syndromes are associated with an increased risk for development of diabetes. Although a discussion of each is beyond the scope of this text, the most commonly associated disorders are discussed here. Both type 1 and type 2 diabetes have been described occurring at an increased frequency in several congenital genetic diagnoses compared to the general population. As these associations have become increasingly recognized, recommendations for screening and treatment have emerged as important components of care in these select populations. In addition, advances in genetic mechanisms for these disorders have brought new genes to light as potential regulators of glucose metabolism and diabetes risk.

DOWN SYNDROME
Down syndrome (DS), or trisomy 21, occurs in just under 1 out of every 700 births in the United States (230). Collectively, the prevalence of diabetes among children and young adults with DS is estimated to be threefold to fourfold higher compared to the general population (231,232,233), though some have estimated close to a tenfold increase (234). Individuals with DS are at an increased risk for autoimmune disorders, including thyroiditis (235), celiac disease (236), and type 1 diabetes, where autoantibodies are present in a greater proportion of children with DS compared to an age-matched healthy population (237). An estimated 0.3%–11% of individuals with DS develop type 1 diabetes (234). A Dutch population study found a prevalence of 3.4 cases per 1,000 individuals below the age of 9 years (232). Although high-risk HLA haplotypes are similar between the DS population and those with type 1 diabetes (237), other mechanisms accounting for the increased risk, including a susceptibility gene on chromosome 21 (238), have been proposed. Type 1 diabetes can occur at any age during childhood or adulthood in DS, but there is a propensity for the onset to occur in younger children compared to the type 1 diabetes population as a whole (239). BMIs in the overweight and obese category are certainly more common in the DS population, but a parallel trend in cases of type 2 diabetes has not been described to this point (240). Perhaps related to this lack of an association with type 2 diabetes, pediatric recommendations have not included routine diabetes screening in the DS population (241).

BARDET-BIEDEL AND ALSTROM SYNDROMES
Bardet-Biedel (BB) syndrome is a heterogeneous ciliopathy, characterized by morbid obesity, retinal cone dystrophy, hypogonadism, and developmental delay (242). BB occurs with an overall prevalence of 1 in 140,000–160,000 newborns, though close to a tenfold increase is observed in Newfoundland, Canada, and in regions of Kuwait (243). BB historically has been associated with insulin resistance and/or diabetes, though most of these data are observational (244,245,246). Data from 2011 suggest that despite increases in measures of visceral adiposity and impairment in leptin signaling, adolescents and young adults do not have evidence for glycemic disturbances or increased measures of insulin resistance (as measured by the homeostasis model assessment of insulin resistance) compared to age- and BMI-matched controls (247). Moreover, patients with BB have upregulation of protective adipokines and anti-inflammatory cytokines that are probable additional factors in promoting enhanced insulin sensitivity and reduced tendency toward diabetes (248). Seventeen genes have been linked to BB, and specific mutations may account for some of the individual variability in insulin resistance within the BB population (247) and perhaps the sporadic cases of diabetes reported.

Alstrom syndrome is a very rare autosomal recessive genetic disorder caused by mutations in ALMS1 (249,250) that shares many phenotypic features of BB, including early-onset obesity and cone-rod retinal dystrophy. As of 2014, over 900 cases had been reported worldwide. Unlike BB, Alstrom syndrome is associated with early development of insulin resistance, components of the metabolic syndrome, and progression to type 2 diabetes in childhood or early adulthood (251,252,253,254). Approximately 68% of patients eventually develop type 2 diabetes, with a mean onset of age 16 years (254).

PRADER-WILLI SYNDROME
Prader-Willi syndrome (PWS) is a genetic imprinting disorder, resulting from loss of a paternal region of chromosome 15. Infants with PWS exhibit poor motor tone, decreased arousal, and failure to thrive, often requiring tube feedings for several weeks to months. This period is followed by progressive obesity characterized by an insatiable appetite and difficult-to-control eating behaviors. Short stature
secondary to deficient GH secretion, delayed puberty, possible central adrenal insufficiency, delayed motor and cognitive development, behavioral difficulties, and sleep disturbances are additional features of this disorder.

Given the severe obese phenotypes in PWS, the prevalence of diabetes has been assessed among adults. Diabetes prevalence has been reported in a range of 7%–24% (255,256,257), a rate that is generally higher than expected for other obese adults. Not surprisingly, the risk of diabetes increases over time and with higher BMI among adults (255). Metabolic studies incorporating oral and intravenous glucose tolerance tests have consistently described a relative hypoinsulinemic state compared to age- and BMI-matched controls, though with lower insulin resistance (258,259,260), which may be driven in part by higher levels of adiponectin. Despite these well-described metabolic abnormalities in adults, frank diabetes has not been reported in registries of children with PWS (261), and only rare case reports of type 2 diabetes (262) or abnormalities in glucose tolerance (261) have been described. Although there certainly appears to be a progressive increase in risk for diabetes as they move into adulthood, risk for type 2 diabetes during childhood does not appear to be significantly different in PWS compared to other obese children (263).

TURNER SYNDROME
Turner syndrome, a genetic disorder arising from complete or partial X monosomy has several well-described phenotypic abnormalities. Compared to the general population, females with Turner syndrome are at an increased risk for a multitude of autoimmune disorders, including autoimmune thyroid disease, juvenile rheumatoid arthritis, vitiligo, psoriasis, inflammatory bowel disease, and celiac disease. A fourfold increased risk for type 1 diabetes was observed in a Danish population (264), whereas other registries have identified no such increase (265,266). This discrepancy may be in part related to the stringency to which a diagnosis of type 1 diabetes is made, including appropriate screening with diabetes autoantibodies.

A severalfold increased risk for both type 2 diabetes and impaired glucose tolerance is known to exist among adult women with Turner syndrome (267). This progression towards diabetes appears to begin early in adolescence. Asymptomatic girls with Turner syndrome are more likely to have abnormalities on an OGTT compared to age- and BMI-matched controls (268). Although an increase in insulin resistance in adolescent girls (269) and adult women (270) has been described, there is growing evidence that an abnormality in beta cell secretory function (271,272) accompanies abnormal glucose tolerance in this population. Risk appears to be greatest among women with a karyotype of isochromosome Xq, followed by complete 45,X,0 or with a deletion of the short arm of the X chromosome (266).

Traditional cardiovascular risk factors, including dyslipidemia, adiposity, hypertension, and insulin resistance appear to occur with greater frequency in this population (272,273) as well, and adult women with Turner syndrome are at greater risk for premature atherosclerotic disease (267).

WILLIAMS SYNDROME
Williams syndrome is characterized by distinctive facial dysmorphism, supravalvular aortic stenosis, developmental delay, and transient infantile hypercalcemia. Williams syndrome results from deletions in the long arm of chromosome 7 (7q11.23), comprising approximately 23–25 genes (274). The prevalence of Williams syndrome is estimated at 1 in 7,500 individuals (275). Within this population, diabetes has been reported at a relatively high prevalence. Among 28 adult Williams syndrome patients (mean age of 36 years) without a previous diagnosis of diabetes, 36% were identified as having diabetes and another 39% with impaired glucose tolerance on OGTT (276). Importantly, this propensity towards a type 2 diabetes phenotype may occur in adolescence and is independent of typical type 2 diabetes risk factors.

UNIQUE POPULATIONS AT RISK FOR DIABETES

TRANSPANT RECIPIENTS
Advances in transplantation medicine have expanded treatment availability to previously untreatable disorders and improved long-term survival rates. However, formerly unrecognized complications and sequelae, including diabetes, have emerged in the posttransplant population. Development of diabetes is a well-described phenomenon in individuals undergoing either solid organ or bone marrow transplantation. Impaired glucose regulation in this population stems from a combination of insulin resistance and insulin secretory deficiency (277,278). Posttransplant diabetes is associated with a significant increase in morbidity (increase in cardiovascular events and loss of graft function) and mortality (279). Given the growing population of transplant recipients, this form of diabetes represents an important entity for prevention and management strategies.

Differences in patient populations, type of procedure performed, and posttransplant medication regimens have made it challenging to estimate the prevalence of posttransplant diabetes and define modifiable risk factors (280). Prevalence of diabetes posttransplant varies, with estimates ranging from 4% to 25% in post-kidney transplant patients and 2% to 25% in liver transplant recipients (280). Diabetes risk increases with time after transplantation (279). Similar to the risks for type 2 diabetes in the general population, older age, positive family history for type 2 diabetes, ethnic background, and obesity are also established risk factors in transplant recipients. Beta cell function can be directly impaired by CMV, and viremia following transplantation has been associated with a significant increase in hyperglycemia (281). Similarly, chronic hepatitis C infection, common in the dialysis population, is associated with an increased risk for diabetes (282).
Several medication classes used to prevent organ rejection have well-established risk profiles for increasing risk of hyperglycemia, either through effects on insulin resistance or directly on beta cell function (see the section Drug and Chemical-Induced Diabetes). Choice of immunosuppressive regimen may help explain up to 74% of the variability in posttransplant diabetes incidence (283). Corticosteroids are perhaps the most widely used class that falls in this category. High doses or prolonged courses required in cases of acute rejection or graft versus host disease increase risk for diabetes. Lower doses of prednisolone (5 mg or less) following kidney transplant reduce the incidence of diabetes without an increase in graft loss (284). Calcineurin inhibitors (cyclosporine, tacrolimus, and sirolimus) have also been associated with an increased risk for diabetes. This class of agents may impart a direct toxic effect to beta cell function. The diabetes risk associated with tacrolimus increases significantly in kidney transplant recipients (Figure 6.5) (279) and is greater than cyclosporine in kidney, liver, and lung transplant recipients (285,286,287,288). Moreover, conversion from tacrolimus to cyclosporine has been associated with resolution of diabetes in both kidney and liver transplant recipients (289,290).

**INTRAUTERINE GROWTH RETARDATION**

Individuals born with a history of growth retardation in utero are at an increased risk for development of type 2 diabetes. An inherent impairment in insulin secretion is present among fetuses and infants with intrauterine growth retardation. This impairment persists over time and can result in significant insulin secretory abnormalities as an adult (291). Low birth weight is associated with a 47% increased risk for type 2 diabetes compared to normal weight births (292). Thus, adults who were born with intrauterine growth retardation and have additional risk factors for type 2 diabetes (e.g., genetic predisposition, factors that increase insulin resistance) are at particular risk for progression to impaired glucose tolerance or type 2 diabetes and should be screened according to ADA standard screening guidelines.

**MALNUTRITION**

Though rarely encountered in the United States, malnutrition can be associated with diabetes. Malnutrition-related diabetes is also known as tropical diabetes, as most individuals with diabetes are from tropical countries. This form of diabetes is most often identified in young, malnourished male adolescents and adults (age 10–30 years) from poverty-stricken, developing countries. Subtypes have been described, delineated by the presence of pancreatic calcifications and variable exocrine deficiency (fibrocalkulous pancreatic diabetes). These patients are both insulin resistant and insulinopenic but do not develop ketoacidosis. Although malnutrition and protein deficiency are believed to be central to pathophysiology, other environmental and genetic factors are also likely to play a role.

**MITOCHONDRIAL DIABETES**

Mitochondrial diabetes represents a rare form of diabetes, stemming from a number of described mutations in mitochondrial DNA, but most often the A3243G mutation. Mitochondrial diabetes accounts for approximately 1% of all cases of diabetes in adults (293,294). There is typically a strong clustering of familial diabetes cases with a maternal transmission pattern. Diabetes presentations can be variable, from an insidious onset similar to a patient with type 2 diabetes to more profound insulin-deficient states. Diabetes onset can occur at a variety of ages but most commonly in early- to mid-adulthood. Mitochondrial diabetes cases are united by the presence of sensorineural hearing impairment in most affected individuals, as well as progressive loss of insulin secretory capacity. Some cases have been identified as part of the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes), though this phenotype is often not present in affected individuals.

**TYPE 1B DIABETES**

Although not considered an immune-mediated form, type 1b diabetes, also referred to as idiopathic or Flatbush diabetes, is marked by severe insulin deficiency and ketoacidosis similar to autoimmune type 1a diabetes. However, this form of diabetes is highlighted by the absence of known diabetes autoantibodies. Type 1b is more frequently identified in males of African American, Indian, Japanese, and Latino descent.
Over a 10-year period, among adults presenting with diabetic ketoacidosis at one medical center, 72% were auto-antibody-negative. Several classification schemes have been developed to better classify this form of diabetes, owing to the relative uncertainty behind the underlying pathophysiology, variable beta cell reserve observed at diagnosis, and presence of ketoacidosis at diagnosis (ketosis-onset) and/or recurrent episodes of ketosis (ketosis-prone) (295,296).

Although insulin is required to manage disease initially, this form of diabetes is also characterized by reversion to insulin independence or only intermittent use over time (297).

CONCLUDING REMARKS

The spectrum of diabetes does not simply extend to individuals with type 1 or type 2 diabetes. Several other congenital and acquired disorders or exposures can lead to abnormal insulin signaling and loss of beta cell function that herald an abnormal rise in blood glucose. Moreover, common forms of type 1 and 2 diabetes can occur on the backdrop of many other congenital and acquired disorders. This heterogeneous collection of patient populations represents only a small fraction of all cases, but collectively and individually, they remain important forms of diabetes.

LIST OF ABBREVIATIONS

A1c . . . . . . . . glycosylated hemoglobin
ADA . . . . . . . American Diabetes Association
AIDS . . . . . . . acquired immune deficiency syndrome
APS . . . . . . . autoimmune polyendocrine syndrome
BB . . . . . . . . Bardet-Biedel syndrome
BMI . . . . . . . body mass index
CF . . . . . . . . cystic fibrosis
CFRD . . . . . . cystic fibrosis-related diabetes
CMV . . . . . . . cytomegalovirus
CP . . . . . . . . chronic pancreatitis
CRS . . . . . . . congenital rubella syndrome
DS . . . . . . . . Down syndrome
FDA . . . . . . . U.S. Food and Drug Administration
GAD . . . . . . . glutamic acid decarboxylase
GH . . . . . . . growth hormone
GLUT . . . . . . glucose transporter
HGP . . . . . . . hereditary/genetic pancreatitis
HIV . . . . . . . human immunodeficiency virus
HLA . . . . . . . human leukocyte antigen
IPEX . . . . . . . immunodysregulation polyendocrinopathy enteropathy X-linked
OGTT . . . . . . oral glucose tolerance test
POEMS . . . . polyeuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes syndrome
PP . . . . . . . . pancreatic polypeptide
PWS . . . . . . . Prader-Willi syndrome
TPIAT . . . . . . total pancreatectomy with islet autotransplantation

CONVERSIONS

Conversions for glucose values are provided in Diabetes in America Appendix 1 Conversions.

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