CHAPTER 6

OTHER SPECIFIC TYPES OF DIABETES

Gregory P. Forlenza, MD, Antoinette Moran, MD, and Brandon Nathan, MD

Dr. Gregory P. Forlenza is Assistant Professor of Pediatrics at the Barbara Davis Center for Diabetes at the University of Colorado School of Medicine, Aurora, CO. Dr. Antoinette Moran is Professor of Pediatrics and Division Head of Pediatric Endocrinology and Dr. Brandon Nathan is Associate Professor of Pediatrics at the University of Minnesota, Minneapolis, MN.

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.

Received in final form March 23, 2016.

INTRODUCTION

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

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

Table 6.1 continues on the next page.

TABLE 6.1. (continued)

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

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.

SOURCE: Original table constructed by G. Forlenza, A. Moran, and B. Nathan.

VIRAL INFECTIONS AND DIABETES

CONGENITAL VIRAL INFECTIONS

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 insulitis 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

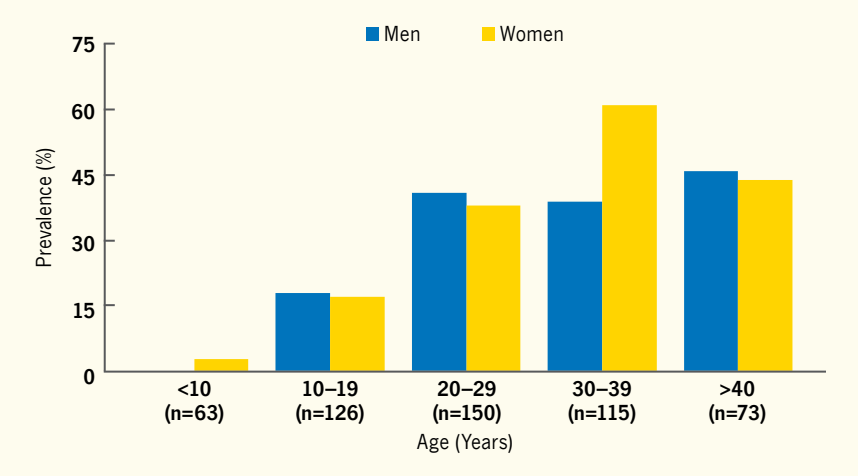
Viral infections occurring after the newborn period have been postulated to play a role in the etiology of diabetes, though this remains a controversial area of study (25,26). Although not completely understood, the proposed viral-mediated mechanisms include the concepts of: molecular mimicry, where 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 insulitis 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.

FIGURE 6.1. Prevalence of Cystic Fibrosis-Related Diabetes, by Age and Sex, 2008



Among 527 patients followed at the University of Minnesota.

SOURCE: Reference 29, copyright © 2009 American Diabetes Association, reprinted with permission from the American Diabetes Association

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

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

SOURCE: Original table constructed by G. Forlenza, A. Moran, and B. Nathan.

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 postprandial 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

documented in these patients compared to 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 necessitates that patients at a minimum achieve ADA goals. Ongoing studies are determining whether even more aggressive goals are appropriate in CF.

DIABETES DUE TO PANCREATITIS AND TOTAL PANCREATECTOMY

DESCRIPTION OF DIABETES DUE TO PANCREATITIS

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).

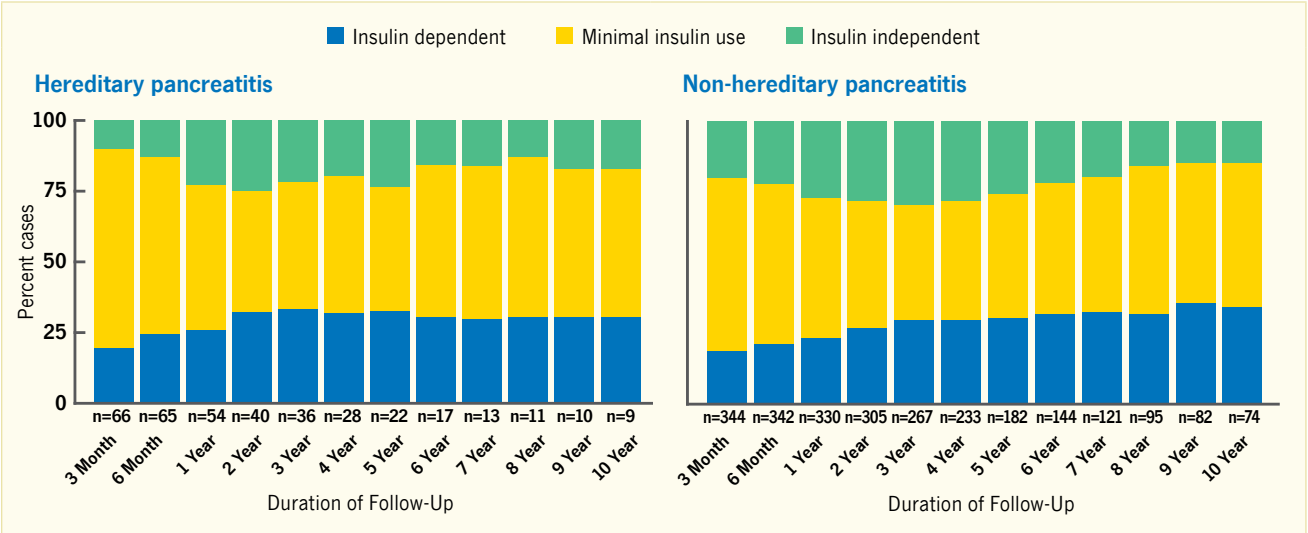
Cohort studies of patients have shown that following TPIAT, 80%–99% of patients denied the presence of pancreatitis pain and >80% denied the presence of any pain (93,95). Significant improvements across all quality-of-life measures have been observed after TPIAT procedure, with >85% of patients indicating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



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).

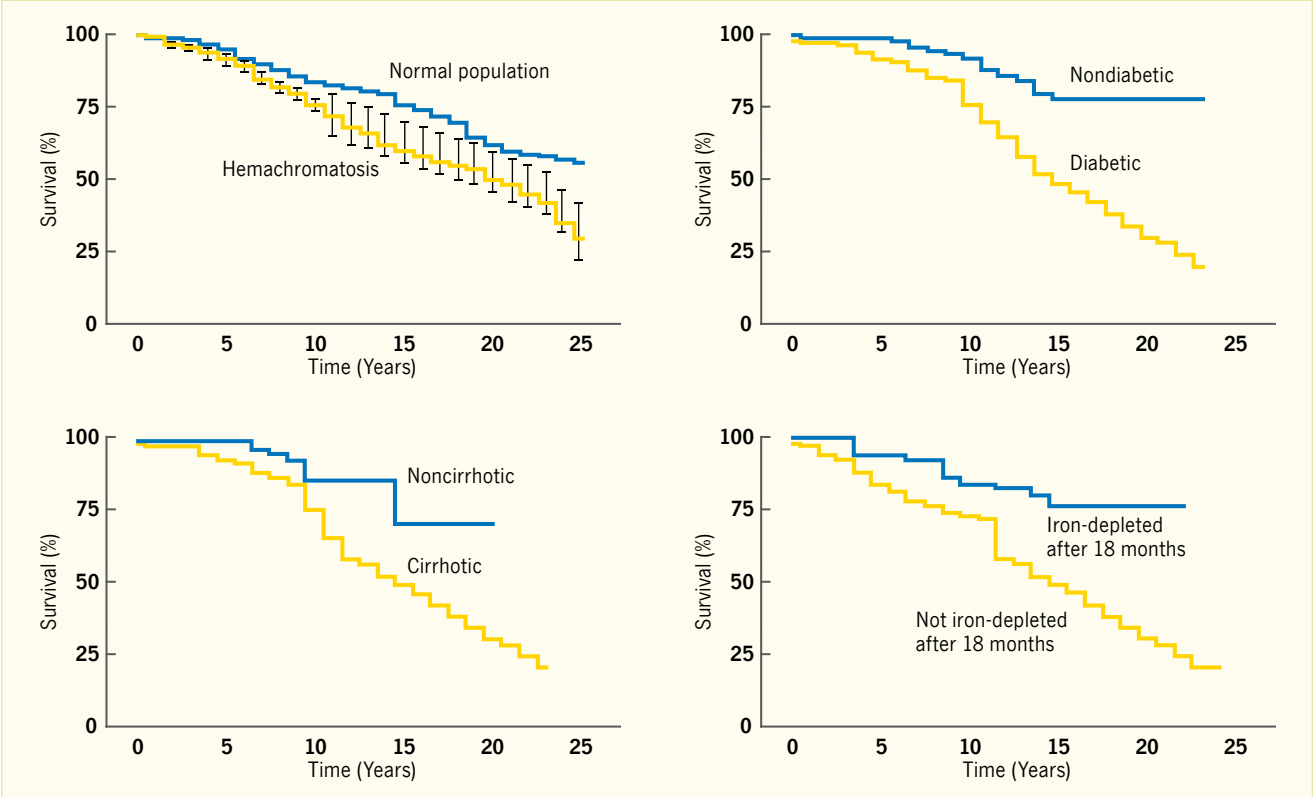
HEMOCHROMATOSIS

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

FIGURE 6.3. Hemochromatosis: Long-Term Survival



The figure shows 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 ($p<0.05$ to <0.002 by log-rank test).

SOURCE: Reference 112, copyright © 1985 Massachusetts Medical Society, reprinted with permission

TABLE 6.3. Genetic Factors Underlying Hereditary Hemochromatosis

TYPE	GENE, INHERITANCE PATTERN	PATHOGENESIS	PRIMARY CLINICAL FEATURE	SEVERITY
Type 1 (classic)	*HFE*, AR	Decreased hepcidin	Liver fibrosis, cirrhosis, onset at age 30–40 years	Variable
Type 2A (juvenile)	*HJV*, AR	Inhibition of hepcidin expression	Cardiomyopathy, hypogonadism, onset at age <30 years	Severe
Type 2B (juvenile)	*HAMP*, AR	Decreased hepcidin	Cardiomyopathy, hypogonadism, onset at age <30 years	Severe
Type 3	*TfR2*, AR	Abnormal sensing of iron, decreased hepcidin	Liver fibrosis, cirrhosis, onset at age 30–40 years	Variable
Type 4	*SLC40A*, AD	Decreased iron export from macrophages, rare hepcidin resistance	Anemia	Mild

AD, autosomal dominant; AR, autosomal recessive.

SOURCE: Reference 113, copyright © 2013 Taylor & Francis, reprinted with permission

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/m^2) 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 hyperglycemia on insulin resistance in patients already diagnosed with diabetes, and ascertainment bias.

Independent associations of decreased insulin sensitivity in patients with type 2 diabetes and increased iron stores have been noted (126). This has led to consideration of whether some patients with type 2 diabetes may have undiagnosed hemochromatosis. Although some small observation studies have identified an increased prevalence of gene mutations in *HFE* among individuals diagnosed with type 2 diabetes (127), in larger case-control studies matched for age, weight, and sex, no such associations have been found (128,129). To this point, there have been no calls to screen for hemochromatosis among the type 2 diabetes population at large. Consideration of screening should be made in individuals with type 2 diabetes and symptoms suggesting iron overload or with a positive family history for hemochromatosis.

Treatment of diabetes in patients with hemochromatosis is complex and is, at least in part, dependent on stage of disease and progression of end-organ failure. 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

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

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.

SOURCE: Original table constructed by G. Forlenza, A. Moran, and B. Nathan.

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.

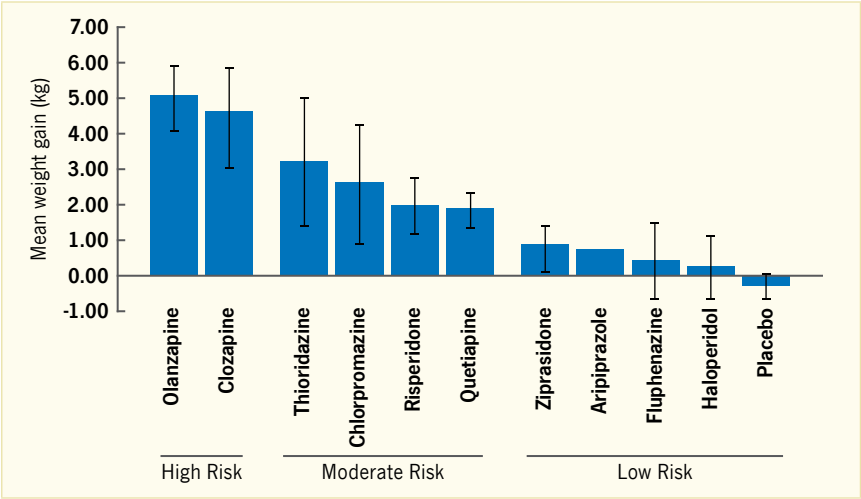
ATYPICAL ANTIPSYCHOTICS

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).

FIGURE 6.4. Meta-Analysis of Weight Gain With Atypical Antipsychotics



Meta-analysis displaying mean and 95% confidence interval for effect of atypical antipsychotics on weight after up to 12 weeks of treatment.

SOURCE: Reference 143, copyright © 2012 Nature Publishing Group, reprinted with permission

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 rosuvastatin (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

TABLE 6.5. Similarities Between the Metabolic Syndrome and Lipodystrophy Due to HIV Highly Active Antiretroviral Therapy

VARIABLE	METABOLIC SYNDROME	HIV-ASSOCIATED LIPODYSTROPHY
Hyperinsulinemia	Present	Present
Dysglycemia	Present	Present
Central adiposity	Present	Present
Hypertension	Present	Present
Atherogenic lipid profile*	Present	Present
Hyperuricemia	Present	Unknown
Prothrombotic state	Present	Present
Proinflammatory state	Present	Present

HIV, human immunodeficiency virus.
* Low high-density lipoprotein (HDL), high triglycerides, and increased small, dense low-density lipoprotein (LDL) particles

SOURCE: Adapted from Reference 164, copyright © 2007 Nature Publishing Group, reprinted with permission

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 ketoacidosis 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/progesterone 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 progesterone, 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/progesterone 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).

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

TYPE 1	TYPE 2
Addison's disease*	Addison's disease*
Alopecia	Alopecia
	Myasthenia gravis
Asplenism	
Autoimmune bronchiolitis	
Autoimmune thyroiditis	Autoimmune thyroiditis*
Chronic active hepatitis	
Chronic candidiasis*	
Dental enamel and nail dystrophy	
	Idiopathic heart block
Ectodermal dysplasia	
Graves' disease	Graves' disease
Hypogonadism	Hypogonadism
Hypoparathyroidism*	Stiff man syndrome
	Parkinson's disease
IgA deficiency	IgA deficiency
	Serositis
Keratitis	
Malabsorption syndrome	Celiac disease, dermatitis herpetiformis
Pernicious anemia	Pernicious anemia
Pure red cell aplasia	
	Idiopathic thrombocytopenia
	Hypophysitis
Type 1 diabetes	Type 1 diabetes*
Vitiligo	Vitiligo

* Primary hallmarks of disease

SOURCE: Adapted from reference 188, copyright © 2014 Elsevier, reprinted with permission

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).

RARE FORMS OF IMMUNE-MEDIATED DIABETES

Distinct from type 1 and type 2 diabetes, the ADA classifies several entities as "other specific types" of diabetes (73). Among these rare forms of diabetes are other types of immune-mediated diabetes, 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 patents 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 excessive 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,O 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

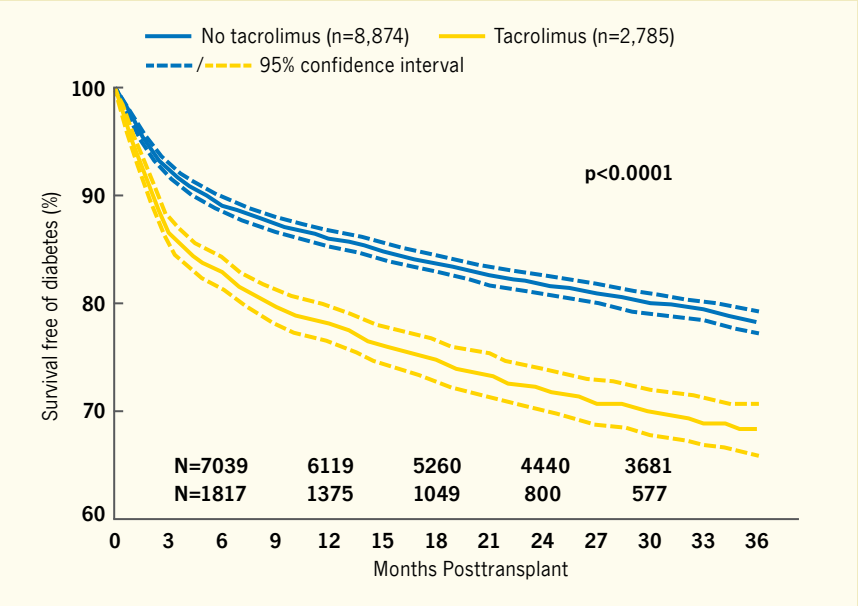
TRANSPLANT RECIPIENTS

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).

FIGURE 6.5. Posttransplant-Associated Diabetes Risk With Use of Tacrolimus



SOURCE: Reference 279, copyright © 2003 John Wiley & Sons, reprinted with permission

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 (fibrocalculous 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 autoantibody-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 . . . . polyneuropathy, 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*.

ACKNOWLEDGMENTS/FUNDING

Dr. Forlenza was supported by a National Institutes of Health (NIH) Training Grant (DK065519) and received research funding from Medtronic Diabetes. Dr. Moran was supported by grants from the National Institute of Diabetes and Digestive and Kidney Diseases (DK101402, DK085476, and DK096518), the National Institute of Allergy and Infectious Diseases (AI015416), and Pfizer. Dr. Nathan received research funding from Medtronic Diabetes.

DUALITY OF INTEREST

Drs. Forlenza, Moran, and Nathan reported no conflicts of interest. Dr. Forlenza served as a consultant for Abbott Diabetes Care. During the time this chapter was written, Dr. Moran held research grants from NIH and Pfizer, did consulting work for Vertex and Minimed Medtronic, and served on a data safety monitoring board for Novo Nordisk.

REFERENCES

1. Centers for Disease Control and Prevention: Elimination of rubella and congenital rubella syndrome—United States, 1969–2004. *MMWR Morb Mortal Wkly Rep* 54:279–282, 2005
2. Berger BE, Omer SB: Could the United States experience rubella outbreaks as a result of vaccine refusal and disease importation? *Hum Vaccin* 6:1016–1020, 2010
3. Banatvala JE, Brown DW: Rubella. *Lancet* 363:1127–1137, 2004
4. Gale EA: Congenital rubella: citation virus or viral cause of type 1 diabetes? *Diabetologia* 51:1559–1566, 2008
5. Ramondetti F, Sacco S, Comelli M, Bruno G, Falorni A, Iannilli A, d'Annunzio G, Iafusco D, Songini M, Toni S, Cherubini V, Carle F; RIDI Study Group: Type 1 diabetes and measles, mumps and rubella childhood infections within the Italian Insulin-dependent Diabetes Registry. *Diabet Med* 29:761–766, 2012
6. Menser MA, Dods L, Harley JD: A twenty-five-year follow-up of congenital rubella. *Lancet* 2:1347–1350, 1967
7. McIntosh ED, Menser MA: A fifty-year follow-up of congenital rubella. *Lancet* 340:414–415, 1992
8. Forrest JM, Turnbull FM, Sholler GF, Hawker RE, Martin FJ, Doran TT, Burgess MA: Gregg's congenital rubella patients 60 years later. *Med J Aust* 177:664–667, 2002
9. Ginsberg-Fellner F, Witt ME, Fedun B, Taub F, Dobersen MJ, McEvoy RC, Cooper LZ, Notkins AL, Rubinstein P: Diabetes mellitus and autoimmunity in patients with the congenital rubella syndrome. *Rev Infect Dis* 7(Suppl 1):S170–S176, 1985
10. Shaver KA, Boughman JA, Nance WE: Congenital rubella syndrome and diabetes: a review of epidemiologic, genetic, and immunologic factors. *Am Ann Deaf* 130:526–532, 1985
11. Fine PE, Adelstein AM, Snowman J, Clarkson JA, Evans SM: Long term effects of exposure to viral infections in utero. *Br Med J (Clin Res Ed)* 290:509–511, 1985
12. Numazaki K, Goldman H, Seemayer TA, Wong I, Wainberg MA: Infection by human cytomegalovirus and rubella virus of cultured human fetal islets of Langerhans. *In Vivo* 4:49–54, 1990
13. McEvoy RC, Fedun B, Cooper LZ, Thomas NM, Rodriguez de Cordoba S, Rubinstein P, Ginsberg-Fellner F: Children at high risk of diabetes mellitus: New York studies of families with diabetes and of children with congenital rubella syndrome. *Adv Exp Med Biol* 246:221–227, 1988
14. Viskari H, Paronen J, Keskinen P, Simell S, Zawilinska B, Zgorniak-Nowosielska I, Korhonen S, Ilonen J, Simell O, Haapala AM, Knip M, Hyoty H: Humoral beta-cell autoimmunity is rare in patients with the congenital rubella syndrome. *Clin Exp Immunol* 133:378–383, 2003
15. Rubinstein P, Walker ME, Fedun B, Witt ME, Cooper LZ, Ginsberg-Fellner F: The HLA system in congenital rubella patients with and without diabetes. *Diabetes* 31:1088–1091, 1982
16. Thorn SR, Rozance PJ, Brown LD, Hay WW, Jr.: The intrauterine growth restriction phenotype: fetal adaptations and potential implications for later life insulin resistance and diabetes. *Semin Reprod Med* 29:225–236, 2011
17. Cannon MJ: Congenital cytomegalovirus (CMV) epidemiology and awareness. *J Clin Virol* 46(Suppl 4):S6–S10, 2009
18. Ward KP, Galloway WH, Auchterlonie IA: Congenital cytomegalovirus infection and diabetes. *Lancet* 1:497, 1979
19. Jenson AB, Rosenberg HS, Notkins AL: Pancreatic islet-cell damage in children with fatal viral infections. *Lancet* 2:354–358, 1980
20. Numazaki K, Goldman H, Wong I, Wainberg MA: Viral infection of human fetal islets of Langerhans. Replication of human cytomegalovirus in cultured human fetal pancreatic islets. *Am J Clin Pathol* 90:52–57, 1988
21. Ivarsson SA, Lindberg B, Nilsson KO, Ahlfors K, Svanberg L: The prevalence of type 1 diabetes mellitus at follow-up of Swedish infants congenitally infected with cytomegalovirus. *Diabet Med* 10:521–523, 1993
22. Aarnisalo J, Veijola R, Vainionpaa R, Simell O, Knip M, Ilonen J: Cytomegalovirus infection in early infancy: risk of induction and progression of autoimmunity associated with type 1 diabetes. *Diabetologia* 51:769–772, 2008
23. Beck RW, Tamborlane WV, Bergenstal RM, Miller KM, DuBose SN, Hall CA; T1D Exchange Clinic Network: The T1D Exchange clinic registry. *J Clin Endocrinol Metab* 97:4383–4389, 2012
24. SEARCH Study Group: SEARCH for Diabetes in Youth: a multicenter study of the prevalence, incidence and classification of diabetes mellitus in youth. *Control Clin Trials* 25:458–471, 2004
25. Atkinson MA, Eisenbarth GS, Michels AW: Type 1 diabetes. *Lancet* 383:69–82, 2014
26. Atkinson MA, Eisenbarth GS: Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 358:221–229, 2001
27. Filippi CM, von Herrath MG: Viral trigger for type 1 diabetes: pros and cons. *Diabetes* 57:2863–2871, 2008
28. Schneider DA, von Herrath MG: Potential viral pathogenic mechanism in human type 1 diabetes. *Diabetologia* 57:2009–2018, 2014
29. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W: Cystic fibrosis-related diabetes: current trends in prevalence, incidence and mortality. *Diabetes Care* 32:1626–1631, 2009
30. Cystic Fibrosis Foundation: Cystic Fibrosis Foundation Patient Registry: 2013 Annual Data Report to the Center Directors. Bethesda, MD, 2013
31. McMullen AH, Pasta DJ, Frederick PD, Konstan MW, Morgan WJ, Schechter MS, Wagener JS: Impact of pregnancy on women with cystic fibrosis. *Chest* 129:706–711, 2006
32. Barak A, Dulitzki M, Efrati O, Augarten A, Szeinberg A, Reichert N, Modan D, Weiss B, Miller M, Katzanelson D, Yahav Y: Pregnancies and outcome in women with cystic fibrosis. *Isr Med Assoc J* 7:95–98, 2005
33. Marshall BC, Butler SM, Stoddard M, Moran AM, Liou TG, Morgan WJ: Epidemiology of cystic fibrosis-related diabetes. *J Pediatr* 146:681–687, 2005
34. Hadjiliadis D, Madill J, Chaparro C, Tsang A, Waddell TK, Singer LG, Hutcheon MA, Keshavjee S, Elizabeth Tullis D: Incidence and prevalence of diabetes mellitus in patients with cystic fibrosis undergoing lung transplantation before and after lung transplantation. *Clin Transplant* 19:773–778, 2005
35. Ntimbane T, Comte B, Mailhot G, Berthiaume Y, Poitout V, Prentki M, Rabasa-Lhoret R, Levy E: Cystic fibrosis-related diabetes: from CFTR dysfunction to oxidative stress. *Clin Biochem Rev* 30:153–177, 2009
36. Blackman SM, Hsu S, Vanscoy LL, Collaco JM, Ritter SE, Naughton K, Cutting GR: Genetic modifiers play a substantial role in diabetes complicating cystic fibrosis. *J Clin Endocrinol Metab* 94:1302–1309, 2009
37. Bellin MD, Laguna T, Leschyshyn J, Regelmann W, Dunitz J, Billings J, Moran A: Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study. *Pediatr Diabetes* 14:417–421, 2013

38. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, Robinson KA, Sabadosa KA, Stecenko A, Slovis B; CFRD Guidelines Committee: Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. *Diabetes Care* 33:2697–2708, 2010
39. HAPO Study Cooperative Research Group; Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA: Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 358:1991–2002, 2008
40. Lanng S, Hansen A, Thorsteinsson B, Nerup J, Koch C: Glucose tolerance in patients with cystic fibrosis: five year prospective study. *BMJ* 311:655–659, 1995
41. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, Tullis E, Liou TG, Allen H; Cystic Fibrosis Related Diabetes Therapy Study Group: Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the Cystic Fibrosis Related Diabetes Therapy Trial. *Diabetes Care* 32:1783–1788, 2009
42. Hameed S, Morton JR, Jaffe A, Field PI, Belessis Y, Yoong T, Katz T, Verge CF: Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. *Diabetes Care* 33:221–226, 2010
43. Suratwala D, Chan JS, Kelly A, Meltzer LJ, Gallagher PR, Traylor J, Rubenstein RC, Marcus CL: Nocturnal saturation and glucose tolerance in children with cystic fibrosis. *Thorax* 66:574–578, 2011
44. Schmid K, Fink K, Holl RW, Hebestreit H, Ballmann M: Predictors for future cystic fibrosis-related diabetes by oral glucose tolerance test. *J Cyst Fibros* 13:80–85, 2014
45. Brodsky J, Dougherty S, Makani R, Rubenstein RC, Kelly A: Elevation of 1-hour plasma glucose during oral glucose tolerance testing is associated with worse pulmonary function in cystic fibrosis. *Diabetes Care* 34:292–295, 2011
46. Schiaffini R, Brufani C, Russo B, Fintini D, Migliaccio A, Pecorelli L, Bizzarri C, Lucidi V, Cappa M: Abnormal glucose tolerance in children with cystic fibrosis: the predictive role of continuous glucose monitoring system. *Eur J Endocrinol* 162:705–710, 2010
47. Kolouskova S, Zemkova D, Bartosova J, Skalicka V, Sumnik Z, Vavrova V, Lebl J: Low-dose insulin therapy in patients with cystic fibrosis and early-stage insulinopenia prevents deterioration of lung function: a 3-year prospective study. *J Pediatr Endocrinol Metab* 24:449–454, 2011
48. Mozzillo E, Franzese A, Valerio G, Sepe A, De Simone I, Mazzarella G, Ferri P, Raia V: One-year glargine treatment can improve the course of lung disease in children and adolescents with cystic fibrosis and early glucose derangements. *Pediatr Diabetes* 10:162–167, 2009
49. Bizzarri C, Lucidi V, Ciampalini P, Bella S, Russo B, Cappa M: Clinical effects of early treatment with insulin glargine in patients with cystic fibrosis and impaired glucose tolerance. *J Endocrinol Invest* 29:RC1–RC4, 2006
50. Hameed S, Morton JR, Field PI, Belessis Y, Yoong T, Katz T, Woodhead HJ, Walker JL, Neville KA, Campbell TA, Jaffe A, Verge CF: Once daily insulin detemir in cystic fibrosis with insulin deficiency. *Arch Dis Child* 97:464–467, 2012
51. Andersen HU, Lanng S, Pressler T, Laugesen CS, Mathiesen ER: Cystic fibrosis-related diabetes: the presence of microvascular diabetes complications. *Diabetes Care* 29:2660–2663, 2006
52. Schwarzenberg SJ, Thomas W, Olsen TW, Grover T, Walk D, Milla C, Moran A: Microvascular complications in cystic fibrosis-related diabetes. *Diabetes Care* 30:1056–1061, 2007
53. Finkelstein SM, Wielinski CL, Elliott GR, Warwick WJ, Barbosa J, Wu SC, Klein DJ: Diabetes mellitus associated with cystic fibrosis. *J Pediatr* 112:373–377, 1988
54. Lanng S, Thorsteinsson B, Nerup J, Koch C: Influence of the development of diabetes mellitus on clinical status in patients with cystic fibrosis. *Eur J Pediatr* 151:684–687, 1992
55. Milla CE, Warwick WJ, Moran A: Trends in pulmonary function in patients with cystic fibrosis correlate with the degree of glucose intolerance at baseline. *Am J Respir Crit Care Med* 162:891–895, 2000
56. Nousia-Arvanitakis S, Galli-Tsinopoulou A, Karamouzis M: Insulin improves clinical status of patients with cystic-fibrosis-related diabetes mellitus. *Acta Paediatr* 90:515–519, 2001
57. Rolon MA, Benali K, Munck A, Navarro J, Clement A, Tubiana-Rufi N, Czernichow P, Polak M: Cystic fibrosis-related diabetes mellitus: clinical impact of prediabetes and effects of insulin therapy. *Acta Paediatr* 90:860–867, 2001
58. Battezzati A, Mari A, Zazzeron L, Alicandro G, Claut L, Battezzati PM, Colombo C: Identification of insulin secretory defects and insulin resistance during oral glucose tolerance test in a cohort of cystic fibrosis patients. *Eur J Endocrinol* 165:69–76, 2011
59. Rosenecker J, Hofler R, Steinkamp G, Eichler I, Smaczny C, Ballmann M, Posselt HG, Bargon J, von der Hardt H: Diabetes mellitus in patients with cystic fibrosis: the impact of diabetes mellitus on pulmonary function and clinical outcome. *Eur J Med Res* 6:345–350, 2001
60. Milla CE, Billings J, Moran A: Diabetes is associated with dramatically decreased survival in female but not male subjects with cystic fibrosis. *Diabetes Care* 28:2141–2144, 2005
61. Sims EJ, Green MW, Mehta A: Decreased lung function in female but not male subjects with established cystic fibrosis-related diabetes. *Diabetes Care* 28:1581–1587, 2005
62. Chamnan P, Shine BS, Haworth CS, Bilton D, Adler AI: Diabetes as a determinant of mortality in cystic fibrosis. *Diabetes Care* 33:311–316, 2010
63. Kien CL, Zipf WB, Horswill CA, Denne SC, McCoy KS, O'Dorisio TM: Effects of feeding on protein turnover in healthy children and in children with cystic fibrosis. *Am J Clin Nutr* 64:608–614, 1996
64. Hardin DS, LeBlanc A, Lukenbaugh S, Para L, Seilheimer DK: Proteolysis associated with insulin resistance in cystic fibrosis. *Pediatrics* 101:433–437, 1998
65. Moran A, Milla C, Ducret R, Nair KS: Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance. *Diabetes* 50:1336–1343, 2001
66. Moran A, Basu R, Milla C, Jensen MD: Insulin regulation of free fatty acid kinetics in adult cystic fibrosis patients with impaired glucose tolerance. *Metabolism* 53:1467–1472, 2004
67. Brennan AL, Gyi KM, Wood DM, Johnson J, Holliman R, Baines DL, Philips BJ, Geddes DM, Hodson ME, Baker EH: Airway glucose concentrations and effect on growth of respiratory pathogens in cystic fibrosis. *J Cyst Fibros* 6:101–109, 2007
68. Ntimbane T, Krishnamoorthy P, Huot C, Legault L, Jacob SV, Brunet S, Levy E, Gueraud F, Lands LC, Comte B: Oxidative stress and cystic fibrosis-related diabetes: a pilot study in children. *J Cyst Fibros* 7:373–384, 2008

69. Hunt WR, Zughaier SM, Guentert DE, Shenep MA, Koval M, McCarty NA, Hansen JM: Hyperglycemia impedes lung bacterial clearance in a murine model of cystic fibrosis-related diabetes. *Am J Physiol Lung Cell Mol Physiol* 306:L43–L49, 2014
70. White H, Morton AM, Peckham DG, Conway SP: Dietary intakes in adult patients with cystic fibrosis—do they achieve guidelines? *J Cyst Fibros* 3:1–7, 2004
71. Cheung MS, Bridges NA, Prasad SA, Francis J, Carr SB, Suri R, Balfour-Lynn IM: Growth in children with cystic fibrosis-related diabetes. *Pediatr Pulmonol* 44:1223–1225, 2009
72. Ripa P, Robertson I, Cowley D, Harris M, Master IB, Cotterill AM: The relationship between insulin secretion, the insulin-like growth factor axis and growth in children with cystic fibrosis. *Clin Endocrinol (Oxf)* 56:383–389, 2002
73. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 37(Suppl 1):S81–S90, 2014
74. Vinik AI, Jackson WP: Endocrine secretions in chronic pancreatitis. In *Secondary Diabetes: The Spectrum of the Diabetic Syndromes*. Podolsky S, Viswanathan M, Eds. New York, Raven Press, 1980, p. 165–189
75. Bank S: Chronic pancreatitis: clinical features and medical management. *Am J Gastroenterol* 81:153–167, 1986
76. Cui Y, Andersen DK: Pancreatogenic diabetes: special considerations for management. *Pancreatology* 11:279–294, 2011
77. Kakrani AL, Paranjpe SM, Kakrani VA: Pancreatic fibrosis-calcification with diabetes in South Maharashtra, India. *Trop Geogr Med* 37:276–278, 1985
78. Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD: Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* 28:338–342, 2012
79. Rickels MR, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, Brand R, Frulloni L, Anderson MA, Whitcomb DC; PancreasFest Recommendation Conference Participants: Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology* 13:336–342, 2013
80. Ewald N, Bretzel RG: Diabetes mellitus secondary to pancreatic diseases (type 3c)—are we neglecting an important disease? *Eur J Intern Med* 24:203–206, 2013
81. Hardt PD, Brendel MD, Kloer HU, Bretzel RG: Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? *Diabetes Care* 31(Suppl 2):S165–S169, 2008
82. Tzetis M, Kaliakatsos M, Fotoulaki M, Papatheodorou A, Doudounakis S, Tsezou A, Makrythanasis P, Kanavakis E, Nousia-Arvanitakis S: Contribution of the CFTR gene, the pancreatic secretory trypsin inhibitor gene (SPINK1) and the cationic trypsinogen gene (PRSS1) to the etiology of recurrent pancreatitis. *Clin Genet* 71:451–457, 2007
83. Knop FK, Vilsboll T, Larsen S, Hojberg PV, Volund A, Madsbad S, Holst JJ, Krarup T: Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. *Am J Physiol Endocrinol Metab* 292:E324–E330, 2007
84. Ewald N, Hardt PD: Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol* 19:7276–7281, 2013
85. Couet C, Genton P, Pointel JP, Louis J, Gross P, Saudax E, Debry G, Drouin P: The prevalence of retinopathy is similar in diabetes mellitus secondary to chronic pancreatitis with or without pancreatectomy and in idiopathic diabetes mellitus. *Diabetes Care* 8:323–328, 1985
86. Schneider MB, Matsuzaki H, Haorah J, Ulrich A, Standop J, Ding XZ, Adrian TE, Pour PM: Prevention of pancreatic cancer induction in hamsters by metformin. *Gastroenterology* 120:1263–1270, 2001
87. Li D, Yeung SC, Hassan MM, Konopleva M, Abbruzzese JL: Antidiabetic therapies affect risk of pancreatic cancer. *Gastroenterology* 137:482–488, 2009
88. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM: New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care* 32:1620–1625, 2009
89. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD: Metformin and reduced risk of cancer in diabetic patients. *BMJ* 330:1304–1305, 2005
90. Etemad B, Whitcomb DC: Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 120:682–707, 2001
91. Howes N, Greenhalf W, Stocken DD, Neoptolemos JP: Cationic trypsinogen mutations and pancreatitis. *Gastroenterol Clin North Am* 33:767–787, 2004
92. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, Truninger K, Ammann R, Cavallini G, Charnley RM, Uomo G, Delhaye M, Spicak J, Drumm B, Jansen J, Mountford R, Whitcomb DC, Neoptolemos JP; European Registry of Hereditary Pancreatitis and Pancreatic Cancer (EUROPAC): Clinical and genetic characteristics of hereditary pancreatitis in Europe. *Clin Gastroenterol Hepatol* 2:252–261, 2004
93. Chinnakotla S, Radosevich DM, Dunn TB, Bellin MD, Freeman ML, Schwarzenberg SJ, Balamurugan AN, Wilhelm J, Bland B, Vickers SM, Beilman GJ, Sutherland DE, Pruett TL: Long-term outcomes of total pancreatectomy and islet auto transplantation for hereditary/genetic pancreatitis. *J Am Coll Surg* 218:530–543, 2014
94. Bellin MD, Freeman ML, Gelrud A, Slivka A, Clavel A, Humar A, Schwarzenberg SJ, Lowe ME, Rickels MR, Whitcomb DC, Matthews JB; PancreasFest Recommendation Conference Participants, Amann S, Andersen DK, Anderson MA, Baillie J, Block G, Brand R, Chari S, Cook M, Cote GA, Dunn T, Frulloni L, Greer JB, Hollingsworth MA, Kim KM, Larson A, Lerch MM, Lin T, Muniraj T, Robertson RP, Sclair S, Singh S, Stopczynski R, Toledo FG, Wilcox CM, Windsor J, Yadav D: Total pancreatectomy and islet autotransplantation in chronic pancreatitis: recommendations from PancreasFest. *Pancreatology* 14:27–35, 2014
95. Sutherland DE, Radosevich DM, Bellin MD, Hering BJ, Beilman GJ, Dunn TB, Chinnakotla S, Vickers SM, Bland B, Balamurugan AN, Freeman ML, Pruett TL: Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg* 214:409–424, 2012
96. Lakey JR, Warnock GL, Shapiro AM, Korbutt GS, Ao Z, Kneteman NM, Rajotte RV: Intraductal collagenase delivery into the human pancreas using syringe loading or controlled perfusion. *Cell Transplant* 8:285–292, 1999
97. Ricordi C, Lacy PE, Scharp DW: Automated islet isolation from human pancreas. *Diabetes* 38(Suppl 1):140–142, 1989
98. Hathout E, Chan NK, Tan A, Sakata N, Mace J, Pearce W, Peverini R, Chinnock R, Sowers L, Obenaus A: In vivo imaging demonstrates a time-line for new vessel formation in islet transplantation. *Pediatr Transplant* 13:892–897, 2009

99. Speier S, Nyqvist D, Cabrera O, Yu J, Molano RD, Pileggi A, Moede T, Kohler M, Wilbertz J, Leibiger B, Ricordi C, Leibiger IB, Caicedo A, Berggren PO: Noninvasive in vivo imaging of pancreatic islet cell biology. *Nat Med* 14:574–578, 2008
100. Forlenza GP, Chinnakotla S, Schwarzenberg SJ, Cook M, Radosevich DM, Manchester C, Gupta S, Nathan B, Bellin MD: Near-euglycemia can be achieved safely in pediatric total pancreatectomy islet autotransplant recipients using an adapted intravenous insulin infusion protocol. *Diabetes Technol Ther* 16:706–713, 2014
101. Finzi G, Davalli A, Placidi C, Usellini L, La Rosa S, Folli F, Capella C: Morphological and ultrastructural features of human islet grafts performed in diabetic nude mice. *Ultrastruct Pathol* 29:525–533, 2005
102. Nacher V, Merino JF, Raurell M, Soler J, Montanya E: Normoglycemia restores beta-cell replicative response to glucose in transplanted islets exposed to chronic hyperglycemia. *Diabetes* 47:192–196, 1998
103. Bellin MD, Sutherland DE, Chinnakotla S, Dunn TY, Kim Y, Johnson J, Saeed A, Manchester C, Balamurugan AN, Hering BJ, Pruett TL, Beilman GJ: Insulin independence after islet autotransplant is associated with subtle differences in early post-transplant glycemic control (Abstract). *Diabetes* 61(Suppl 1):A43, 2012
104. Bellin MD, Sutherland DE: Pediatric islet autotransplantation: indication, technique, and outcome. *Curr Diab Rep* 10:326–331, 2010
105. Everhart J, Wright D: Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. *JAMA* 273:1605–1609, 1995
106. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M: Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* 92:2076–2083, 2005
107. Ben Q, Xu M, Ning X, Liu J, Hong S, Huang W, Zhang H, Li Z: Diabetes mellitus and risk of pancreatic cancer: a meta-analysis of cohort studies. *Eur J Cancer* 47:1928–1937, 2011
108. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM: Probability of pancreatic cancer following diabetes: a population-based study. *Gastroenterology* 129:504–511, 2005
109. Whitcomb DC: Inflammation and cancer V. Chronic pancreatitis and pancreatic cancer. *Am J Physiol Gastrointest Liver Physiol* 287:G315–G319, 2004
110. Yeo TP: Demographics, epidemiology, and inheritance of pancreatic ductal adenocarcinoma. *Semin Oncol* 42:8–18, 2015
111. Morrison M: Pancreatic cancer and diabetes. *Adv Exp Med Biol* 771:229–239, 2012
112. Niederau C, Fischer R, Sonnenberg A, Stremmel W, Trampisch HJ, Strohmeyer G: Survival and causes of death in cirrhotic and in noncirrhotic patients with primary hemochromatosis. *N Engl J Med* 313:1256–1262, 1985
113. Kanwar P, Kowdley KV: Diagnosis and treatment of hereditary hemochromatosis: an update. *Expert Rev Gastroenterol Hepatol* 7:517–530, 2013
114. Hanson EH, Imperatore G, Burke W: HFE gene and hereditary hemochromatosis: a HuGE review. Human Genome Epidemiology. *Am J Epidemiol* 154:193–206, 2001
115. Buysschaert M, Paris I, Selvais P, Hermans MP: Clinical aspects of diabetes secondary to idiopathic haemochromatosis in French-speaking Belgium. *Diabetes Metab* 23:308–313, 1997
116. Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y: Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 127:105–110, 1997
117. McClain DA, Abraham D, Rogers J, Brady R, Gault P, Ajioka R, Kushner JP: High prevalence of abnormal glucose homeostasis secondary to decreased insulin secretion in individuals with hereditary haemochromatosis. *Diabetologia* 49:1661–1669, 2006
118. Utzschneider KM, Kowdley KV: Hereditary hemochromatosis and diabetes mellitus: implications for clinical practice. *Nat Rev Endocrinol* 6:26–33, 2010
119. O'Sullivan EP, McDermott JH, Murphy MS, Sen S, Walsh CH: Declining prevalence of diabetes mellitus in hereditary haemochromatosis—the result of earlier diagnosis. *Diabetes Res Clin Pract* 81:316–320, 2008
120. Pack-Mabien A, Brown B, Herbert DE, Haynes J, Jr.: Iron overload in adults with sickle cell disease who have received intermittent red blood cell transfusions. *J Am Assoc Nurse Pract* 27:591–596, 2015
121. Cunningham MJ, Macklin EA, Neufeld EJ, Cohen AR; Thalassemia Clinical Research Network: Complications of beta-thalassemia major in North America. *Blood* 104:34–39, 2004
122. Majhail NS, DeFor T, Lazarus HM, Burns LJ: High prevalence of iron overload in adult allogeneic hematopoietic cell transplant survivors. *Biol Blood Marrow Transplant* 14:790–794, 2008
123. Hramiak IM, Finegood DT, Adams PC: Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med* 20:110–118, 1997
124. Dubois-Laforgue D, Caillat-Zucman S, Boitard C, Timsit J: Clinical characteristics of type 2 diabetes in patients with mutations of HFE. *Diabetes Metab* 26:65–68, 2000
125. Cooksey RC, Jouihan HA, Ajioka RS, Hazel MW, Jones DL, Kushner JP, McClain DA: Oxidative stress, beta-cell apoptosis, and decreased insulin secretory capacity in mouse models of hemochromatosis. *Endocrinology* 145:5305–5312, 2004
126. Fernandez-Real JM, Penarroja G, Castro A, Garcia-Bragado F, Hernandez-Aguado I, Ricart W: Blood letting in high-ferritin type 2 diabetes: effects on insulin sensitivity and beta-cell function. *Diabetes* 51:1000–1004, 2002
127. Salonen JT, Tuomainen TP, Kontula K: Role of C282Y mutation in haemochromatosis gene in development of type 2 diabetes in healthy men: prospective cohort study. *BMJ* 320:1706–1707, 2000
128. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T: Penetrance of 845G→A (C282Y) HFE hereditary haemochromatosis mutation in the USA. *Lancet* 359:211–218, 2002
129. Halsall DJ, McFarlane I, Luan J, Cox TM, Wareham NJ: Typical type 2 diabetes mellitus and HFE gene mutations: a population-based case-control study. *Hum Mol Genet* 12:1361–1365, 2003
130. Abraham D, Rogers J, Gault P, Kushner JP, McClain DA: Increased insulin secretory capacity but decreased insulin sensitivity after correction of iron overload by phlebotomy in hereditary haemochromatosis. *Diabetologia* 49:2546–2551, 2006
131. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL: Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. Atherosclerosis Risk in Communities Study. *N Engl J Med* 342:905–912, 2000
132. Hwang JL, Weiss RE: Steroid-induced diabetes: a clinical and molecular approach to understanding and treatment. *Diabetes Metab Res Rev* 30:96–102, 2014
133. Kwon S, Hermayer KL: Glucocorticoid-induced hyperglycemia. *Am J Med Sci* 345:274–277, 2013

134. Harris D, Barts A, Connors J, Dahl M, Elliott T, Kong J, Keane T, Thompson D, Stafford S, Ur E, Sirrs S: Glucocorticoid-induced hyperglycemia is prevalent and unpredictable for patients undergoing cancer therapy: an observational cohort study. *Curr Oncol* 20:e532–e538, 2013
135. Hirsch IB, Paauw DS: Diabetes management in special situations. *Endocrinol Metab Clin North Am* 26:631–645, 1997
136. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J: Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med* 154:97–101, 1994
137. Yasuda K, Hines E, 3rd, Kitabchi AE: Hypercortisolism and insulin resistance: comparative effects of prednisone, hydrocortisone, and dexamethasone on insulin binding of human erythrocytes. *J Clin Endocrinol Metab* 55:910–915, 1982
138. Clore JN, Thurby-Hay L: Glucocorticoid-induced hyperglycemia. *Endocr Pract* 15:469–474, 2009
139. Kim SY, Yoo CG, Lee CT, Chung HS, Kim YW, Han SK, Shim YS, Yim JJ: Incidence and risk factors of steroid-induced diabetes in patients with respiratory disease. *J Korean Med Sci* 26:264–267, 2011
140. Simmons LR, Molyneaux L, Yue DK, Chua EL: Steroid-induced diabetes: is it just unmasking of type 2 diabetes? *ISRN Endocrinol* 2012:910905, 2012
141. Morrato EH, Newcomer JW, Kamat S, Baser O, Harnett J, Cuffel B: Metabolic screening after the American Diabetes Association's consensus statement on antipsychotic drugs and diabetes. *Diabetes Care* 32:1037–1042, 2009
142. Lean ME, Pajonk FG: Patients on atypical antipsychotic drugs: another high-risk group for type 2 diabetes. *Diabetes Care* 26:1597–1605, 2003
143. Lett TA, Wallace TJ, Chowdhury NI, Tiwari AK, Kennedy JL, Muller DJ: Pharmacogenetics of antipsychotic-induced weight gain: review and clinical implications. *Mol Psychiatry* 17:242–266, 2012
144. Elliott WJ, Meyer PM: Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. *Lancet* 369:201–207, 2007
145. Bangalore S, Parkar S, Grossman E, Messerli FH: A meta-analysis of 94,492 patients with hypertension treated with beta blockers to determine the risk of new-onset diabetes mellitus. *Am J Cardiol* 100:1254–1262, 2007
146. Shen L, Shah BR, Reyes EM, Thomas L, Wojdyla D, Diem P, Leiter LA, Charbonnel B, Mareev V, Horton ES, Haffner SM, Soska V, Holman R, Bethel MA, Schaper F, Sun JL, McMurray JJ, Califf RM, Krum H: Role of diuretics, β blockers, and statins in increasing the risk of diabetes in patients with impaired glucose tolerance: reanalysis of data from the NAVIGATOR study. *BMJ* 347:f6745, 2013
147. Pollare T, Lithell H, Selinus I, Berne C: Sensitivity to insulin during treatment with atenolol and metoprolol: a randomised, double blind study of effects on carbohydrate and lipoprotein metabolism in hypertensive patients. *BMJ* 298:1152–1157, 1989
148. Goldner MG, Zarowitz H, Akgun S: Hyperglycemia and glycosuria due to thiazide derivatives administered in diabetes mellitus. *N Engl J Med* 262:403–405, 1960
149. Zillich AJ, Garg J, Basu S, Bakris GL, Carter BL: Thiazide diuretics, potassium, and the development of diabetes: a quantitative review. *Hypertension* 48:219–224, 2006
150. Carter BL, Einhorn PT, Brands M, He J, Cutler JA, Whelton PK, Bakris GL, Brancati FL, Cushman WC, Oparil S, Wright JT, Jr.; Working Group from the National Heart, Lung, and Blood Institute: Thiazide-induced dysglycemia: call for research from a working group from the National Heart, Lung, and Blood Institute. *Hypertension* 52:30–36, 2008
151. Carlsen JE, Kober L, Torp-Pedersen C, Johansen P: Relation between dose of bendrofluazide, antihypertensive effect, and adverse biochemical effects. *BMJ* 300:975–978, 1990
152. Sukhija R, Prayaga S, Marashdeh M, Bursac Z, Kakar P, Bansal D, Sachdeva R, Kesan SH, Mehta JL: Effect of statins on fasting plasma glucose in diabetic and nondiabetic patients. *J Investig Med* 57:495–499, 2009
153. Freeman DJ, Norrie J, Sattar N, Neely RD, Cobbe SM, Ford I, Isles C, Lorimer AR, Macfarlane PW, McKillop JH, Packard CJ, Shepherd J, Gaw A: Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. *Circulation* 103:357–362, 2001
154. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I: Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. *Lancet* 375:735–742, 2010
155. Simsek S, Schalkwijk CG, Wolffenbuttel BH: Effects of rosuvastatin and atorvastatin on glycaemic control in type 2 diabetes—the CORALL study. *Diabet Med* 29:628–631, 2012
156. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM: Risk of incident diabetes among patients treated with statins: population based study. *BMJ* 346:f2610, 2013
157. Nowis D, Malenda A, Furs K, Oleszczak B, Sadowski R, Chlebowska J, Firczuk M, Bujnicki JM, Staruch AD, Zagozdzon R, Glodkowska-Mrowka E, Szablewski L, Golab J: Statins impair glucose uptake in human cells. *BMJ Open Diabetes Res Care* 2:e000017, 2014
158. Sazonov V, Maccubbin D, Sisk CM, Canner PL: Effects of niacin on the incidence of new onset diabetes and cardiovascular events in patients with normoglycaemia and impaired fasting glucose. *Int J Clin Pract* 67:297–302, 2013
159. Ding Y, Li Y, Wen A: Effect of niacin on lipids and glucose in patients with type 2 diabetes: a meta-analysis of randomized, controlled clinical trials. *Clin Nutr* 34:838–844, 2015
160. Elam MB, Hunninghake DB, Davis KB, Garg R, Johnson C, Egan D, Kostis JB, Sheps DS, Brinton EA: Effect of niacin on lipid and lipoprotein levels and glycemic control in patients with diabetes and peripheral arterial disease: the ADMIT study: a randomized trial. Arterial Disease Multiple Intervention Trial. *JAMA* 284:1263–1270, 2000
161. Koh Y, Bidstrup H, Nichols DL: Niacin increased glucose, insulin, and C-peptide levels in sedentary nondiabetic postmenopausal women. *Int J Womens Health* 6:913–920, 2014
162. Tripathi A, Liese AD, Jerrell JM, Zhang J, Rizvi AA, Albrecht H, Duffus WA: Incidence of diabetes mellitus in a population-based cohort of HIV-infected and non-HIV-infected persons: the impact of clinical and therapeutic factors over time. *Diabet Med* 31:1185–1193, 2014
163. Rasmussen LD, Mathiesen ER, Kronborg G, Pedersen C, Gerstoft J, Obel N: Risk of diabetes mellitus in persons with and without HIV: a Danish nationwide population-based cohort study. *PLOS ONE* 7:e44575, 2012

164. Falutz J: Therapy insight: body-shape changes and metabolic complications associated with HIV and highly active antiretroviral therapy. *Nat Clin Pract Endocrinol Metab* 3:651–661, 2007
165. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, El-Sadr W, Monforte AD, Fontas E, Law MG, Friis-Moller N, Phillips A; Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study: Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. *Diabetes Care* 31:1224–1229, 2008
166. Perronne C, Bricaire F, Leport C, Assan D, Vilde JL, Assan R: Hypoglycaemia and diabetes mellitus following parenteral pentamidine mesylate treatment in AIDS patients. *Diabet Med* 7:585–589, 1990
167. Herchline TE, Plouffe JF, Para MF: Diabetes mellitus presenting with ketoacidosis following pentamidine therapy in patients with acquired immunodeficiency syndrome. *J Infect* 22:41–44, 1991
168. Assan R, Perronne C, Assan D, Chotard L, Mayaud C, Matheron S, Zucman D: Pentamidine-induced derangements of glucose homeostasis. Determinant roles of renal failure and drug accumulation. A study of 128 patients. *Diabetes Care* 18:47–55, 1995
169. Uzzan B, Bentata M, Campos J, Mosnier A, Krivitzky A, Perret GY, Modigliani E: Effects of aerosolized pentamidine on glucose homeostasis and insulin secretion in HIV-positive patients: a controlled study. *AIDS* 9:901–907, 1995
170. Abs R, Feldt-Rasmussen U, Mattsson AF, Monson JP, Bengtsson BA, Goth MI, Wilton P, Koltowska-Haggstrom M: Determinants of cardiovascular risk in 2589 hypopituitary GH-deficient adults—a KIMS database analysis. *Eur J Endocrinol* 155:79–90, 2006
171. Colao A, Ferone D, Marzullo P, Lombardi G: Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 25:102–152, 2004
172. Cutfield WS, Wilton P, Bennmarker H, Albertsson-Wikland K, Chatelain P, Ranke MB, Price DA: Incidence of diabetes mellitus and impaired glucose tolerance in children and adolescents receiving growth-hormone treatment. *Lancet* 355:610–613, 2000
173. Child CJ, Zimmermann AG, Scott RS, Cutler GB, Jr., Battelino T, Blum WF, GeNeSIS International Advisory Board: Prevalence and incidence of diabetes mellitus in GH-treated children and adolescents: analysis from the GeNeSIS observational research program. *J Clin Endocrinol Metab* 96:E1025–E1034, 2011
174. Luger A, Mattsson AF, Koltowska-Haggstrom M, Thunander M, Goth M, Verhelst J, Abs R: Incidence of diabetes mellitus and evolution of glucose parameters in growth hormone-deficient subjects during growth hormone replacement therapy: a long-term observational study. *Diabetes Care* 35:57–62, 2012
175. Reed ML, Merriam GR, Kargi AY: Adult growth hormone deficiency—benefits, side effects, and risks of growth hormone replacement. *Front Endocrinol (Lausanne)* 4:64, 2013
176. Hannon TS, Danadian K, Suprasongsin C, Arslanian SA: Growth hormone treatment in adolescent males with idiopathic short stature: changes in body composition, protein, fat, and glucose metabolism. *J Clin Endocrinol Metab* 92:3033–3039, 2007
177. Hokken-Koelega AC, De Waal WJ, Sas TC, Van Pareren Y, Arends NJ: Small for gestational age (SGA): endocrine and metabolic consequences and effects of growth hormone treatment. *J Pediatr Endocrinol Metab* 17(Suppl 3):463–469, 2004
178. Dahlgren J: Metabolic benefits of growth hormone therapy in idiopathic short stature. *Horm Res Paediatr* 76(Suppl 3):56–58, 2011
179. Perlman JA, Russell-Briefel R, Ezzati T, Lieberknecht G: Oral glucose tolerance and the potency of contraceptive progestins. *J Chronic Dis* 38:857–864, 1985
180. Lopez LM, Grimes DA, Schulz KF: Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. *Cochrane Database Syst Rev* 4:CD006133, 2014
181. Jones J, Mosher W, Daniels K: Current contraceptive use in the United States, 2006–2010, and changes in patterns of use since 1995. *Natl Health Stat Report* 60:1–25, 2012
182. Chasan-Taber L, Willett WC, Stampfer MJ, Hunter DJ, Colditz GA, Spiegelman D, Manson JE: A prospective study of oral contraceptives and NIDDM among U.S. women. *Diabetes Care* 20:330–335, 1997
183. Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B, Hennekens CH, Speizer FE: Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. *Diabetologia* 35:967–972, 1992
184. Gourdy P: Diabetes and oral contraception. *Best Pract Res Clin Endocrinol Metab* 27:67–76, 2013
185. Bodin J, Stene LC, Nygaard UC: Can exposure to environmental chemicals increase the risk of diabetes type 1 development? *Biomed Res Int* 2015:208947, 2015
186. Meo SA, Memon AN, Sheikh SA, Rouq FA, Usmani AM, Hassan A, Arian SA: Effect of environmental air pollution on type 2 diabetes mellitus. *Eur Rev Med Pharmacol Sci* 19:123–128, 2015
187. Michels AW, Gottlieb PA: Autoimmune polyglandular syndromes. *Nat Rev Endocrinol* 6:270–277, 2010
188. Cutolo M: Autoimmune polyendocrine syndromes. *Autoimmun Rev* 13:85–89, 2014
189. Dittmar M, Kahaly GJ: Polyglandular autoimmune syndromes: immunogenetics and long-term follow-up. *J Clin Endocrinol Metab* 88:2983–2992, 2003
190. Ten S, New M, Maclaren N: Clinical review 130: Addison's disease 2001. *J Clin Endocrinol Metab* 86:2909–2922, 2001
191. Lindmark E, Chen Y, Georgoudaki AM, Dudziak D, Lindh E, Adams WC, Lore K, Winqvist O, Chambers BJ, Karlsson MC: AIRE expressing marginal zone dendritic cells balances adaptive immunity and T-follicular helper cell recruitment. *J Autoimmun* 42:62–70, 2013
192. Gombos Z, Hermann R, Kiviniemi M, Nejentsev S, Reimand K, Fadeyev V, Peterson P, Uibo R, Ilonen J: Analysis of extended human leukocyte antigen haplotype association with Addison's disease in three populations. *Eur J Endocrinol* 157:757–761, 2007
193. Myhre AG, Undlien DE, Lovas K, Uhlving S, Nedrebo BG, Fougner KJ, Trovik T, Sorheim JI, Husebye ES: Autoimmune adrenocortical failure in Norway autoantibodies and human leukocyte antigen class II associations related to clinical features. *J Clin Endocrinol Metab* 87:618–623, 2002
194. Rottembourg D, Deal C, Lambert M, Mallone R, Carel JC, Lacroix A, Caillat-Zucman S, le Deist F: 21-hydroxylase epitopes are targeted by CD8 T cells in autoimmune Addison's disease. *J Autoimmun* 35:309–315, 2010
195. Husebye ES, Anderson MS: Autoimmune polyendocrine syndromes: clues to type 1 diabetes pathogenesis. *Immunity* 32:479–487, 2010
196. Verbsky JW, Chatila TA: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related

disorders: an evolving web of heritable autoimmune diseases. *Curr Opin Pediatr* 25:708–714, 2013
197. Josefowicz SZ, Lu LF, Rudensky AY: Regulatory T cells: mechanisms of differentiation and function. *Ann Rev Immunol* 30:531–564, 2012
198. Benoist C, Mathis D: Treg cells, life history, and diversity. *Cold Spring Harb Perspect Biol* 4:a007021, 2012
199. Moraes-Vasconcelos D, Costa-Carvalho BT, Torgerson TR, Ochs HD: Primary immune deficiency disorders presenting as autoimmune diseases: IPEX and APECED. *J Clin Immunol* 28(Suppl 1):S11–S19, 2008
200. Savova R, Arshinkova M, Houghton J, Konstantinova M, Gaydarova M, Georgieva E, Popova G, Genova V, Tomova N, Anadoliiska A, Koprivarova K: Clinical case of immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome with severe immune deficiency and late onset of endocrinopathy and enteropathy. *Case Rep Med* 2014:564926, 2014
201. McKeon A, Robinson MT, McEvoy KM, Matsumoto JY, Lennon VA, Ahlskog JE, Pittock SJ: Stiff-man syndrome and variants: clinical course, treatments, and outcomes. *Arch Neurol* 69:230–238, 2012
202. Zhang S, Wang G, Wang J: Type B insulin resistance syndrome induced by systemic lupus erythematosus and successfully treated with intravenous immunoglobulin: case report and systematic review. *Clin Rheumatol* 32:181–188, 2013
203. Rosenstein ED, Advani S, Reitz RE, Kramer N: The prevalence of insulin receptor antibodies in patients with systemic lupus erythematosus and related conditions. *J Clin Rheumatol* 7:371–373, 2001
204. Dreval AV, Trigolosova IV, Misnikova IV, Kovalyova YA, Tishenina RS, Barsukov IA, Vinogradova AV, Wolffenbuttel BH: Prevalence of diabetes mellitus in patients with acromegaly. *Endocr Connect* 3:93–98, 2014
205. Nabarro JD: Acromegaly. *Clin Endocrinol (Oxf)* 26:481–512, 1987
206. Boden G, Soeldner JS, Steinke J, Thorn GW: Serum human growth hormone (HGH) response to IV glucose: diagnosis of acromegaly in females and males. *Metabolism* 17:1–9, 1968
207. Sonksen PH, Greenwood FC, Ellis JP, Lowy C, Rutherford A, Nabarro JD: Changes of carbohydrate tolerance in acromegaly with progress of the disease and in response to treatment. *J Clin Endocrinol Metab* 27:1418–1430, 1967
208. Resmini E, Minuto F, Colao A, Ferone D: Secondary diabetes associated with principal endocrinopathies: the impact of new treatment modalities. *Acta Diabetol* 46:85–95, 2009
209. van Raalte DH, Ouwens DM, Diamant M: Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? *Eur J Clin Invest* 39:81–93, 2009
210. Mazziotti G, Gazzaruso C, Giustina A: Diabetes in Cushing syndrome: basic and clinical aspects. *Trends Endocrinol Metab* 22:499–506, 2011
211. Clayton RN, Raskauskiene D, Reulen RC, Jones PW: Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. *J Clin Endocrinol Metab* 96:632–642, 2011
212. Gurwitz JH, Bohn RL, Glynn RJ, Monane M, Mogun H, Avorn J: Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch Intern Med* 154:97–101, 1994
213. Henriksen JE, Alford F, Ward GM, Beck-Nielsen H: Risk and mechanism of dexamethasone-induced deterioration of glucose tolerance in non-diabetic first-degree relatives of NIDDM patients. *Diabetologia* 40:1439–1448, 1997
214. Darmon P, Dadoun F, Boullu-Ciocca S, Grino M, Alessi MC, Dutour A: Insulin resistance induced by hydrocortisone is increased in patients with abdominal obesity. *Am J Physiol Endocrinol Metab* 291:E995–E1002, 2006
215. Donihi AC, Raval D, Saul M, Korytkowski MT, DeVita MA: Prevalence and predictors of corticosteroid-related hyperglycemia in hospitalized patients. *Endocr Pract* 12:358–362, 2006
216. Wiesner TD, Bluher M, Windgassen M, Paschke R: Improvement of insulin sensitivity after adrenalectomy in patients with pheochromocytoma. *J Clin Endocrinol Metab* 88:3632–3636, 2003
217. Turnbull DM, Johnston DG, Alberti KG, Hall R: Hormonal and metabolic studies in a patient with a pheochromocytoma. *J Clin Endocrinol Metab* 51:930–933, 1980
218. Stenstrom G, Sjostrom L, Smith U: Diabetes mellitus in phaeochromocytoma. Fasting blood glucose levels before and after surgery in 60 patients with phaeochromocytoma. *Acta Endocrinol (Copenh)* 106:511–515, 1984
219. La Batide-Alanore A, Chatellier G, Plouin PF: Diabetes as a marker of pheochromocytoma in hypertensive patients. *J Hypertens* 21:1703–1707, 2003
220. Vance JE, Buchanan KD, O'Hara D, Williams RH, Porte D, Jr.: Insulin and glucagon responses in subjects with pheochromocytoma: effect of alpha adrenergic blockade. *J Clin Endocrinol Metab* 29:911–916, 1969
221. Reincke M, Meisinger C, Holle R, Quinkler M, Hahner S, Beuschlein F, Bidlingmaier M, Seissler J, Endres S, Participants of the German Conn's Registry: Is primary aldosteronism associated with diabetes mellitus? Results of the German Conn's Registry. *Horm Metab Res* 42:435–439, 2010
222. Sowers JR, Whaley-Connell A, Epstein M: Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 150:776–783, 2009
223. Yang L, Shen X, Yan S, Yuan X, Lu J, Wei W: HbA1c in the diagnosis of diabetes and abnormal glucose tolerance in patients with Graves' hyperthyroidism. *Diabetes Res Clin Pract* 101:28–34, 2013
224. Roubsanthisuk W, Watanakejorn P, Tunlakit M, Sriussadaporn S: Hyperthyroidism induces glucose intolerance by lowering both insulin secretion and peripheral insulin sensitivity. *J Med Assoc Thai* 89(Suppl 5):S133–S140, 2006
225. Wang C: The relationship between type 2 diabetes mellitus and related thyroid diseases. *J Diabetes Res* 2013:390534, 2013
226. Nesi G, Marcucci T, Rubio CA, Brandi ML, Tonelli F: Somatostatinoma: clinico-pathological features of three cases and literature reviewed. *J Gastroenterol Hepatol* 23:521–526, 2008
227. Ito T, Igarashi H, Jensen RT: Pancreatic neuroendocrine tumors: clinical features, diagnosis and medical treatment: advances. *Best Pract Res Clin Gastroenterol* 26:737–753, 2012
228. Schusdziarra V: [Glucagonoma—somatostatinoma]. [Article in German] *Z Gastroenterol* (Suppl 1):33–35, 1999
229. Gandhi GY, Basu R, Dispenzieri A, Basu A, Montori VM, Brennan MD: Endocrinopathy in POEMS syndrome: the Mayo Clinic experience. *Mayo Clin Proc* 82:836–842, 2007
230. Parker SE, Mai CT, Canfield MA, Rickard R, Wang Y, Meyer RE, Anderson P, Mason CA, Collins JS, Kirby RS, Correa A; National Birth Defects Prevention Network: Updated national birth prevalence estimates for selected birth defects in the United States, 2004–2006. *Birth Defects Res A Clin Mol Teratol* 88:1008–1016, 2010

231. Goldacre MJ, Wotton CJ, Seagroatt V, Yeates D: Cancers and immune related diseases associated with Down's syndrome: a record linkage study. *Arch Dis Child* 89:1014–1017, 2004
232. Van Goor JC, Massa GG, Hirasing R: Increased incidence and prevalence of diabetes mellitus in Down's syndrome. *Arch Dis Child* 77:186, 1997
233. Bergholdt R, Eising S, Nerup J, Pociot F: Increased prevalence of Down's syndrome in individuals with type 1 diabetes in Denmark: a nationwide population-based study. *Diabetologia* 49:1179–1182, 2006
234. Anwar AJ, Walker JD, Frier BM: Type 1 diabetes mellitus and Down's syndrome: prevalence, management and diabetic complications. *Diabet Med* 15:160–163, 1998
235. Karlsson B, Gustafsson J, Hedov G, Ivarsson SA, Anneren G: Thyroid dysfunction in Down's syndrome: relation to age and thyroid autoimmunity. *Arch Dis Child* 79:242–245, 1998
236. George EK, Mearin ML, Bouquet J, von Blomberg BM, Stapel SO, van Elburg RM, de Graaf EA: High frequency of celiac disease in Down syndrome. *J Pediatr* 128:555–557, 1996
237. Gillespie KM, Dix RJ, Williams AJ, Newton R, Robinson ZF, Bingley PJ, Gale EA, Shield JP: Islet autoimmunity in children with Down's syndrome. *Diabetes* 55:3185–3188, 2006
238. Concannon P, Onengut-Gumuscu S, Todd JA, Smyth DJ, Pociot F, Bergholdt R, Akolkar B, Erlich HA, Hilner JE, Julier C, Morahan G, Nerup J, Nierras CR, Chen WM, Rich SS; Type 1 Diabetes Genetics Consortium: A human type 1 diabetes susceptibility locus maps to chromosome 21q22.3. *Diabetes* 57:2858–2861, 2008
239. Rohrer TR, Hennes P, Thon A, Dost A, Grabert M, Rami B, Wiegand S, Holl RW; DPV Initiative: Down's syndrome in diabetic patients aged <20 years: an analysis of metabolic status, glycaemic control and autoimmunity in comparison with type 1 diabetes. *Diabetologia* 53:1070–1075, 2010
240. Esbensen AJ: Health conditions associated with aging and end of life of adults with Down syndrome. *Int Rev Res Ment Retard* 39:107–126, 2010
241. Bull MJ; Committee on Genetics: Health supervision for children with Down syndrome. *Pediatrics* 128:393–406, 2011
242. Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, Heath O, McManamon PJ, O'Leary E, Pryse-Phillips W: The cardinal manifestations of Bardet-Biedl syndrome, a form of Laurence-Moon-Biedl syndrome. *N Engl J Med* 321:1002–1009, 1989
243. GeneReviews: Bardet-Beidl syndrome [article online], 2015. Available from *http://www.ncbi.nlm.nih.gov/books/NBK1363*. Accessed 23 March 2016
244. Schmidt F, Kapellen TM, Wiegand S, Herbst A, Wolf J, Frohlich-Reiterer EE, Rabl W, Rohrer T, Holl RW; DPV-Wiss Study Group; BMBF Competence Network Diabetes: Diabetes mellitus in children and adolescents with genetic syndromes. *Exp Clin Endocrinol Diabetes* 120:579–585, 2012
245. Iannello S, Bosco P, Cavaleri A, Camuto M, Milazzo P, Belfiore F: A review of the literature of Bardet-Biedl disease and report of three cases associated with metabolic syndrome and diagnosed after the age of fifty. *Obes Rev* 3:123–135, 2002
246. Escallon F, Traboulsi EI, Infante R: A family with the Bardet-Biedl syndrome and diabetes mellitus. *Arch Ophthalmol* 107:855–857, 1989
247. Feuillan PP, Ng D, Han JC, Sapp JC, Wetsch K, Spaulding E, Zheng YC, Caruso RC, Brooks BP, Johnston JJ, Yanovski JA, Biesecker LG: Patients with Bardet-Biedl syndrome have hyperleptinemia suggestive of leptin resistance. *J Clin Endocrinol Metab* 96:E528–E535, 2011
248. Marion V, Mockel A, De Melo C, Obringer C, Claussmann A, Simon A, Messaddeq N, Durand M, Dupuis L, Loeffler JP, King P, Mutter-Schmidt C, Petrovsky N, Stoetzel C, Dollfus H: BBS-induced ciliary defect enhances adipogenesis, causing paradoxical higher-insulin sensitivity, glucose usage, and decreased inflammatory response. *Cell Metab* 16:363–377, 2012
249. Hearn T, Renforth GL, Spalluto C, Hanley NA, Piper K, Brickwood S, White C, Connolly V, Taylor JF, Russell-Eggitt I, Bonneau D, Walker M, Wilson DI: Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. *Nat Genet* 31:79–83, 2002
250. Collin GB, Marshall JD, Ikeda A, So WV, Russell-Eggitt I, Maffei P, Beck S, Boerkoel CF, Sicolo N, Martin M, Nishina PM, Naggert JK: Mutations in ALMS1 cause obesity, type 2 diabetes and neurosensory degeneration in Alstrom syndrome. *Nat Genet* 31:74–78, 2002
251. Bettini V, Maffei P, Pagano C, Romano S, Milan G, Favaretto F, Marshall JD, Paisey R, Scolari F, Greggio NA, Tosetto I, Naggert JK, Sicolo N, Vettor R: The progression from obesity to type 2 diabetes in Alstrom syndrome. *Pediatr Diabetes* 13:59–67, 2012
252. Minton JA, Owen KR, Ricketts CJ, Crabtree N, Shaikh G, Ehtisham S, Porter JR, Carey C, Hodge D, Paisey R, Walker M, Barrett TG: Syndromic obesity and diabetes: changes in body composition with age and mutation analysis of ALMS1 in 12 United Kingdom kindreds with Alstrom syndrome. *J Clin Endocrinol Metab* 91:3110–3116, 2006
253. Marshall JD, Beck S, Maffei P, Naggert JK: Alstrom syndrome. *Eur J Hum Genet* 15:1193–1202, 2007
254. Marshall JD, Bronson RT, Collin GB, Nordstrom AD, Maffei P, Paisey RB, Carey C, Macdermott S, Russell-Eggitt I, Shea SE, Davis J, Beck S, Shatirishvili G, Mihai CM, Hoeltzenbein M, Pozzan GB, Hopkinson I, Sicolo N, Naggert JK, Nishina PM: New Alstrom syndrome phenotypes based on the evaluation of 182 cases. *Arch Intern Med* 165:675–683, 2005
255. Sinnema M, Maaskant MA, van Schrojenstein Lantman-de Valk HM, van Nieuwpoort IC, Drent ML, Curfs LM, Schrander-Stumpel CT: Physical health problems in adults with Prader-Willi syndrome. *Am J Med Genet A* 155A:2112–2124, 2011
256. Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T: Prevalence of, and risk factors for, physical ill-health in people with Prader-Willi syndrome: a population-based study. *Dev Med Child Neurol* 44:248–255, 2002
257. Vogels A, Fryns JP: Age at diagnosis, body mass index and physical morbidity in children and adults with the Prader-Willi syndrome. *Genet Couns* 15:397–404, 2004
258. Haqq AM, Muehlbauer M, Svetkey LP, Newgard CB, Purnell JQ, Grambow SC, Freemark MS: Altered distribution of adiponectin isoforms in children with Prader-Willi syndrome (PWS): association with insulin sensitivity and circulating satiety peptide hormones. *Clin Endocrinol (Oxf)* 67:944–951, 2007
259. Schuster DP, Osei K, Zipf WB: Characterization of alterations in glucose and insulin metabolism in Prader-Willi subjects. *Metabolism* 45:1514–1520, 1996
260. Talebizadeh Z, Butler MG: Insulin resistance and obesity-related factors in Prader-Willi syndrome: comparison with obese subjects. *Clin Genet* 67:230–239, 2005

261. Diene G, Mimoun E, Feigerlova E, Caula S, Molinas C, Grandjean H, Tauber M; French Reference Centre for PWS: Endocrine disorders in children with Prader-Willi syndrome—data from 142 children of the French database. *Horm Res Paediatr* 74:121–128, 2010
262. Sills IN, Rapaport R: Non-insulin dependent diabetes mellitus in a prepubertal child with Prader-Willi syndrome. *J Pediatr Endocrinol Metab* 11:281–282, 1998
263. Brambilla P, Crino A, Bedogni G, Bosio L, Cappa M, Corrias A, Delvecchio M, Di Candia S, Gargantini L, Grechi E, Iughetti L, Mussa A, Ragusa L, Sacco M, Salvatoni A, Chiumello G, Grugni G; Genetic Obesity Study Group of the Italian Society of Pediatric Endocrinology and Diabetology (ISPED): Metabolic syndrome in children with Prader-Willi syndrome: the effect of obesity. *Nutr Metab Cardiovasc Dis* 21:269–276, 2011
264. Jorgensen KT, Rostgaard K, Bache I, Biggar RJ, Nielsen NM, Tommerup N, Frisch M: Autoimmune diseases in women with Turner's syndrome. *Arthritis Rheum* 62:658–666, 2010
265. Bolar K, Hoffman AR, Maneatis T, Lippe B: Long-term safety of recombinant human growth hormone in Turner syndrome. *J Clin Endocrinol Metab* 93:344–351, 2008
266. Bakalov VK, Cheng C, Zhou J, Bondy CA: X-chromosome gene dosage and the risk of diabetes in Turner syndrome. *J Clin Endocrinol Metab* 94:3289–3296, 2009
267. Gravholt CH, Juul S, Naeraa RW, Hansen J: Morbidity in Turner syndrome. *J Clin Epidemiol* 51:147–158, 1998
268. Polychronakos C, Letarte J, Collu R, Ducharme JR: Carbohydrate intolerance in children and adolescents with Turner syndrome. *J Pediatr* 96:1009–1014, 1980
269. Caprio S, Boulware S, Diamond M, Sherwin RS, Carpenter TO, Rubin K, Amiel S, Press M, Tamborlane WV: Insulin resistance: an early metabolic defect of Turner's syndrome. *J Clin Endocrinol Metab* 72:832–836, 1991
270. Salgin B, Amin R, Yuen K, Williams RM, Murgatroyd P, Dunger DB: Insulin resistance is an intrinsic defect independent of fat mass in women with Turner's syndrome. *Horm Res* 65:69–75, 2006
271. Bakalov VK, Cooley MM, Quon MJ, Luo ML, Yanovski JA, Nelson LM, Sullivan G, Bondy CA: Impaired insulin secretion in the Turner metabolic syndrome. *J Clin Endocrinol Metab* 89:3516–3520, 2004
272. O'Gorman CS, Syme C, Lang J, Bradley TJ, Wells GD, Hamilton JK: An evaluation of early cardiometabolic risk factors in children and adolescents with Turner syndrome. *Clin Endocrinol (Oxf)* 78:907–913, 2013
273. Mortensen KH, Andersen NH, Hjerrild BE, Horlyck A, Stochholm K, Hojbjerg Gravholt C: Carotid intima-media thickness is increased in Turner syndrome: multifactorial pathogenesis depending on age, blood pressure, cholesterol and oestrogen treatment. *Clin Endocrinol (Oxf)* 77:844–851, 2012
274. Morris CA: Introduction: Williams syndrome. *Am J Med Genet C Semin Med Genet* 154C:203–208, 2010
275. Stromme P, Bjornstad PG, Ramstad K: Prevalence estimation of Williams syndrome. *J Child Neurol* 17:269–271, 2002
276. Pober BR, Wang E, Caprio S, Petersen KF, Brandt C, Stanley T, Osborne LR, Dzuria J, Gulanski B: High prevalence of diabetes and pre-diabetes in adults with Williams syndrome. *Am J Med Genet C Semin Med Genet* 154C:291–298, 2010
277. Nam JH, Mun JI, Kim SI, Kang SW, Choi KH, Park K, Ahn CW, Cha BS, Song YD, Lim SK, Kim KR, Lee HC, Huh KB: Beta-cell dysfunction rather than insulin resistance is the main contributing factor for the development of post-renal transplantation diabetes mellitus. *Transplantation* 71:1417–1423, 2001
278. Hjelmesaeth J, Hagen M, Hartmann A, Midtvedt K, Egeland T, Jenssen T: The impact of impaired insulin release and insulin resistance on glucose intolerance after renal transplantation. *Clin Transplant* 16:389–396, 2002
279. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ: Diabetes mellitus after kidney transplantation in the United States. *Am J Transplant* 3:178–185, 2003
280. Gomes MB, Cobas RA: Post-transplant diabetes mellitus. *Diabetol Metab Syndr* 1:14, 2009
281. Leung Ki EL, Venetz JP, Meylan P, Lamoth F, Ruiz J, Pascual M: Cytomegalovirus infection and new-onset post-transplant diabetes mellitus. *Clin Transplant* 22:245–249, 2008
282. Yildiz A, Tutuncu Y, Yazici H, Akkaya V, Kayacan SM, Sever MS, Carin M, Karsidag K: Association between hepatitis C virus infection and development of posttransplantation diabetes mellitus in renal transplant recipients. *Transplantation* 74:1109–1113, 2002
283. Montori VM, Basu A, Erwin PJ, Velosa JA, Gabriel SE, Kudva YC: Posttransplantation diabetes: a systematic review of the literature. *Diabetes Care* 25:583–592, 2002
284. Midtvedt K, Hjelmesaeth J, Hartmann A, Lund K, Paulsen D, Egeland T, Jenssen T: Insulin resistance after renal transplantation: the effect of steroid dose reduction and withdrawal. *J Am Soc Nephrol* 15:3233–3239, 2004
285. Fan Y, Xiao YB, Weng YG: Tacrolimus versus cyclosporine for adult lung transplant recipients: a meta-analysis. *Transplant Proc* 41:1821–1824, 2009
286. Kamar N, Mariat C, Delahousse M, Dantal J, Al Najjar A, Cassuto E, Lefrancois N, Cointault O, Touchard G, Villemain F, Di Giambattista F, Benhamou PY; Diapason Study Group: Diabetes mellitus after kidney transplantation: a French multicentre observational study. *Nephrol Dial Transplant* 22:1986–1993, 2007
287. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC: Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. *BMJ* 331:810, 2005
288. Vincenti F, Friman S, Scheuermann E, Rostaing L, Jenssen T, Campistol JM, Uchida K, Pescovitz MD, Marchetti P, Tuncer M, Citterio F, Wiecek A, Chadban S, El-Shahawy M, Budde K, Goto N; DIRECT (Diabetes Incidence after Renal Transplantation: Neoral C Monitoring Versus Tacrolimus) Investigators: Results of an international, randomized trial comparing glucose metabolism disorders and outcome with cyclosporine versus tacrolimus. *Am J Transplant* 7:1506–1514, 2007
289. Ghisdal L, Bouchta NB, Broeders N, Crenier L, Hoang AD, Abramowicz D, Wissing KM: Conversion from tacrolimus to cyclosporine A for new-onset diabetes after transplantation: a single-centre experience in renal transplanted patients and review of the literature. *Transpl Int* 21:146–151, 2008
290. Dumortier J, Bernard S, Bouffard Y, Boillot O: Conversion from tacrolimus to cyclosporine in liver transplanted patients with diabetes mellitus. *Liver Transpl* 12:659–664, 2006
291. Jensen CB, Storgaard H, Dela F, Holst JJ, Madsbad S, Vaag AA: Early differential defects of insulin secretion and action in 19-year-old Caucasian men who had low birth weight. *Diabetes* 51:1271–1280, 2002
292. Harder T, Rodekamp E, Schellong K, Dudenhausen JW, Plagemann A: Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. *Am J Epidemiol* 165:849–857, 2007

293. Maassen JA, 'T Hart LM, Van Essen E, Heine RJ, Nijpels G, Jahangir Tafrechi RS, Raap AK, Janssen GM, Lemkes HH: Mitochondrial diabetes: molecular mechanisms and clinical presentation. *Diabetes* 53(Suppl 1):S103–S109, 2004
294. Martikainen MH, Ronnemaa T, Majamaa K: Prevalence of mitochondrial diabetes in southwestern Finland: a molecular epidemiological study. *Acta Diabetol* 50:737–741, 2013
295. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M: Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev* 29:292–302, 2008
296. Liu B, Yu C, Li Q, Li L: Ketosis-onset diabetes and ketosis-prone diabetes: same or not? *Int J Endocrinol* 2013:821403, 2013
297. American Diabetes Association: (2) Classification and diagnosis of diabetes. *Diabetes Care* 38(Suppl 1):S8–S16, 2015