the insulin receptor. These receptor autoantibodies may block insulin binding or may stimulate the insulin receptor, leading to intermittent hypoglycemia.

Polycystic ovary syndrome (PCOS) is a common disorder that affects premenopausal women and is characterized by chronic anovulation and hyperandrogenism (Chap. 412). Insulin resistance is seen in a significant subset of women with PCOS, and the disorder substantially increases the risk for type 2 DM, independent of the effects of obesity.

Prevention Type 2 DM is preceded by a period of IGT or IFG, and a number of lifestyle modifications and pharmacologic agents prevent or delay the onset of DM. Individuals with prediabetes or increased risk of diabetes should be referred to a structured program to reduce body weight and increase physical activity as well as being screened for cardiovascular disease. The Diabetes Prevention Program (DPP) demonstrated that intensive changes in lifestyle (diet and exercise for 30 min/d five times/week) in individuals with IGT prevented or delayed the development of type 2 DM by 58% compared to placebo. This effect was seen in individuals regardless of age, sex, or ethnic group. In the same study, metformin prevented or delayed diabetes by 31% compared to placebo. The lifestyle intervention group lost 5–7% of their body weight during the 3 years of the study. Studies in Finnish and Chinese populations noted similar efficacy of diet and exercise in preventing or delaying type 2 DM. A number of agents, including α-glucosidase inhibitors, metformin, thiazolidinediones, GLP-1 receptor pathway modifiers, and orlistat, prevent or delay type 2 DM but are not approved for this purpose. Individuals with a strong family history of type 2 DM and individuals with IFG or IGT should be strongly encouraged to maintain a normal BMI and engage in regular physical activity. Pharmacologic therapy for individuals with prediabetes is currently controversial because its cost-effectiveness and safety profile are not known. The ADA has suggested that metformin be considered in individuals with both IFG and IGT who are at very high risk for progression to diabetes (age <60 years, BMI ≥35 kg/m^2, family history of diabetes in first-degree relative, and women with a history of GDM). Individuals with IFG, IGT, or an HbA_{1c} of 5.7–6.4% should be monitored annually to determine if diagnostic criteria for diabetes are present.

GENETICALLY DEFINED, MONOGENIC FORMS OF DIABETES MELLITUS RELATED TO REDUCED INSULIN SECRETION

Several monogenic forms of DM have been identified. More than 10 different variants of MODY, caused by mutations in genes encoding islet-enriched transcription factors or glucokinase (Fig. 417-5; Table 417-1), are transmitted as autosomal dominant disorders. MODY 1, MODY 3, and MODY 5 are caused by mutations in hepatocyte nuclear transcription factor (HNF) 4α, HNF-1α, and HNF-1β, respectively. As their names imply, these transcription factors are expressed in the liver but also in other tissues, including the pancreatic islets and kidney. These factors most likely affect islet development or the expression of genes important in glucose-stimulated insulin secretion or the maintenance of beta cell mass. For example, individuals with an HNF-1α mutation (MODY 3) have a progressive decline in glycemic control but may respond to sulfonylureas. In fact, some of these patients were initially thought to have type 1 DM but were later shown to respond to a sulfonylurea, and insulin was discontinued. Individuals with a HNF-1β mutation have progressive impairment of insulin secretion and hepatic insulin resistance, and require insulin treatment (minimal response to sulfonylureas). These individuals often have other abnormalities such as renal cysts, mild pancreatic exocrine insufficiency, and abnormal liver function tests. Individuals with MODY 2, the result of mutations in the glucokinase gene, have mild-to-moderate, stable hyperglycemia that does not respond to oral hypoglycemic agents. Glucokinase catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is important for glucose sensing by the beta cells (Fig. 417-5) and for glucose utilization by the liver. As a result of glucokinase mutations, higher glucose levels are required to elicit insulin secretory responses, thus altering the set point for insulin secretion. Studies of populations with type 2 DM suggest that mutations in MODY-associated genes are an uncommon (<5%) cause of type 2 DM. Mutations in mitochondrial DNA are associated with diabetes and deafness.

Transient or permanent neonatal diabetes (onset <12 months of age) occurs. Permanent neonatal diabetes may be caused by several genetic mutations, usually requires treatment with insulin, and phenotypically is similar to type 1 DM. Mutations in the ATP-sensitive potassium channel subunits (Kir6.2 and ABCC8) and the insulin gene (interfere with proinsulin folding and processing) (Fig. 417-5) are the major causes of permanent neonatal diabetes. Although these activating mutations in the ATP-sensitive potassium channel subunits impair glucose-stimulated insulin secretion, these individuals may respond to sulfonylureas and can be treated with these agents. These mutations are often associated with a spectrum of neurologic dysfunction. MODY 4 is a rare variant caused by mutations in the insulin promoter factor (IPF) 1, a transcription factor that regulates pancreatic development and insulin gene transcription. Homozygous inactivating mutations cause pancreatic agenesis, whereas heterozygous mutations may result in DM. Mutations in the transcription factor of *GATA6* are the most common cause of pancreatic agenesis. Homozygous glucokinase mutations cause a severe form of neonatal diabetes.

APPROACH TO THE PATIENT: Diabetes Mellitus

Once the diagnosis of DM is made, attention should be directed to symptoms related to diabetes (acute and chronic) and classifying the type of diabetes. DM and its complications produce a wide range of symptoms and signs; those secondary to acute hyperglycemia may occur at any stage of the disease, whereas those related to chronic hyperglycemia begin to appear during the second decade of hyperglycemia (Chap. 419). Individuals with previously undetected type 2 DM may present with chronic complications of DM at the time of diagnosis. The history and physical examination should assess for symptoms or signs of acute hyperglycemia and should screen for the chronic complications and conditions associated with DM.

HISTORY

A complete medical history should be obtained with special emphasis on DM-relevant aspects such as weight, family history of DM and its complications, risk factors for cardiovascular disease, exercise, smoking, and ethanol use. Symptoms of hyperglycemia include polyuria, polydipsia, weight loss, fatigue, weakness, blurry vision, frequent superficial infections (vaginitis, fungal skin infections), and slow healing of skin lesions after minor trauma. Metabolic derangements relate mostly to hyperglycemia (osmotic diuresis) and to the catabolic state of the patient (urinary loss of glucose and calories, muscle breakdown due to protein degradation and decreased protein synthesis). Blurred vision results from changes in the water content of the lens and resolves as the hyperglycemia is controlled.

In a patient with established DM, the initial assessment should also include special emphasis on prior diabetes care, including the type of therapy, prior HbA_{1c} levels, self-monitoring blood glucose results, frequency of hypoglycemia, presence of DM-specific complications, and assessment of the patient's knowledge about diabetes, exercise, and nutrition. Diabetes-related complications may afflict several organ systems, and an individual patient may exhibit some, all, or none of the symptoms related to the complications of DM (Chap. 419). In addition, the presence of DM-related comorbidities should be sought (cardiovascular disease, hypertension, dyslipidemia). Pregnancy plans should be ascertained in women of childbearing age.

PHYSICAL EXAMINATION

In addition to a complete physical examination, special attention should be given to DM-relevant aspects such as weight or BMI,