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Diabetes Mellitus

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Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM exist and are caused by a complex interaction of genetics, environmental factors, and life-style choices. Depending on the etiology of the DM, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production. The metabolic dysregulation associated with DM causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. In the United States, DM is the leading cause of end-stage renal disease (ESRD), nontraumatic lower extremity amputations, and adult blindness. With an increasing incidence worldwide, DM will be a leading cause of morbidity and mortality for the foreseeable future.

CLASSIFICATION

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy (Fig. 323-1). The two broad categories of DM are designated type 1 and type 2 (Table 323-1). Type 1A DM results from autoimmune beta cell destruction, which leads to insulin deficiency. Individuals with type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta cells. However, they develop insulin deficiency by unknown mechanisms and are ketosis prone. Relatively few patients with type 1 DM are in the type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage.

FIGURE 323-1 Spectrum of glucose homeostasis and diabetes mellitus (DM). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG) and 2-h plasma glucose (PG), after a glucose challenge for the different categories of glucose tolerance, are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. Some types of DM may or may not require insulin for survival, hence the dotted line. (Conventional units are used in the figure.) *(Adapted from American Diabetes Association, 2004.)*

TABLE 323-1 Etiologic Classification of Diabetes Mellitus

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
A. Immune-mediated
B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III. Other specific types of diabetes
A. Genetic defects of β-cell function characterized by mutations in:

1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
2. Glucokinase (MODY 2)
3. HNF-1α (MODY 3)
4. Insulin promoter factor (IPF) 1 (MODY 4)
5. HNF-1β (MODY 5)
6. NeuroD1 (MODV6)
7. Mitochondrial DNA
8. Proinsulin or insulin conversion

B. Genetic defects in insulin action

1. Type A insulin resistance
2. Leprechaunism
3. Rabson-Mendenhall syndrome
4. Lipodystrophy syndromes

C.Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy
D.Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
E.Drug- or chemical-induced—Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α- interferon, protease inhibitors, clozapine, beta blockers
F.Infections—congenital rubella, cytomegalovirus, coxsackie
G.Uncommon forms of immune-mediated diabetes—“stiff-man” syndrome, anti-insulin receptor antibodies
H.Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Note: MODY, maturity onset of diabetes of the young.
Source: Adapted from American Diabetes Association, 2004.

Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM (see below). Distinct pathogenic processes in

type 2 DM have important potential therapeutic implications, as pharmacologic agents that target specific metabolic derangements

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have become available. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

Two features of the current classification of DM diverge from previous classifications. First, the terms *insulin-dependent diabetes mellitus* (IDDM) and *noninsulin-dependent diabetes mellitus* (NIDDM) are obsolete. Since many individuals with type 2 DM eventually require insulin treatment for control of glycemia, the use of the term NIDDM generated considerable confusion. A second difference is that age is not a criterion in the classification system. Although type 1 DM most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. It is estimated that between 5 and 10% of individuals who develop DM after age 30 have type 1A DM. Likewise, type 2 DM more typically develops with increasing age, but it also occurs in children, particularly in obese adolescents.

OTHER TYPES OF DM

Other etiologies for DM include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, mitochondrial abnormalities, and a host of conditions that impair glucose tolerance (Table 323-1). *Maturity onset diabetes of the young* (MODY) is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia, and impairment in insulin secretion (discussed below). Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

DM can result from pancreatic exocrine disease when the majority of pancreatic islets (>80%) are destroyed. Hormones that antagonize the action of insulin can lead to DM. Thus, DM is often a feature of endocrinopathies, such as acromegaly and Cushing's disease. Viral infections have been implicated in pancreatic islet destruction, but are an extremely rare cause of DM. Congenital rubella greatly increases the risk for DM; however, most of these individuals also have immunologic markers indicative of autoimmune beta cell destruction.

GESTATIONAL DIABETES MELLITUS (GDM)

Glucose intolerance may develop during pregnancy. Insulin resistance related to the metabolic changes of late pregnancy increases insulin requirements and may lead to IGT. GDM occurs in approximately 4% of pregnancies in the United States; most women revert to normal glucose tolerance post-partum but have a substantial risk (30 to 60%) of developing DM later in life.

EPIDEMIOLOGY

The worldwide prevalence of DM has risen dramatically over the past two decades. Likewise, prevalence rates of IFG are also increasing. Although the prevalence of both type

1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is expected to rise more rapidly in the future because of increasing obesity and reduced activity levels. DM increases with aging. In 2000, the prevalence of DM was estimated to be 0.19% in people <20 years old and 8.6% in people >20 years old. In individuals >65 years the prevalence of DM was 20.1%. The prevalence is similar in men and women throughout most age ranges but is slightly greater in men >60 years.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. Scandinavia has the highest incidence of type 1 DM (e.g., in Finland, the incidence is 35/100,000 per year). The Pacific Rim has a much lower rate (in Japan and China, the incidence is 1 to 3/100,000 per year) of type 1 DM; Northern Europe and the United States share an intermediate rate (8 to 17/100,000 per year). Much of the increased risk of type 1 DM is believed to reflect the frequency of high-risk HLA alleles among ethnic groups in different geographic locations. The prevalence of type 2 DM and its harbinger, IGT, is highest in certain Pacific islands, intermediate in countries such as India and the United States, and relatively low in Russia and China. This variability is likely due to genetic, behavioral, and environmental factors. DM prevalence also varies among different ethnic populations within a given country. In 2000, the prevalence of DM in the United States was 13% in African Americans, 10.2% in Hispanic Americans, 15.5% in Native Americans (American Indians and Alaska natives), and 7.8% in non-Hispanic whites. The onset of type 2 DM occurs, on average, at an earlier age in ethnic groups other than non-Hispanic whites.

DIAGNOSIS

The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM (Table 323-2) based on the following premises: (1) the spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load varies among normal individuals,

and (2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations from a population-based mean. For example, the prevalence of retinopathy in Native Americans (Pima Indian population) begins to increase at a FPG > 6.4 mmol/L (116 mg/dL) (Fig. 323-2).

TABLE 323-2 Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a]
- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b]
- Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

[a] Random is defined as without regard to time since the last meal.

[b] Fasting is defined as no caloric intake for at least 8 h.

[c] The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.

Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.

Source: Modified from American Diabetes Association, 2004.

FIGURE 323-2 Relationship of diabetes-specific complication and glucose tolerance. This figure shows the incidence of retinopathy in Pima Indians as a function of the fasting plasma glucose (FPG), the 2-h plasma glucose after a 75-g oral glucose challenge (2-h PG), or glycated hemoglobin (A1C). Note that the incidence of retinopathy greatly increases at a fasting plasma glucose >116 mg/dL, or a 2-h plasma glucose of 185 mg/dL, or a A1C >6.0%. (Conventional units for blood glucose are used in the figure.) *(Copyright 2002, American Diabetes Association. From Diabetes Care 25(Suppl 1): S5–S20, 2002.)*

Glucose tolerance is classified into three categories based on the FPG: (1) FPG < 5.6 mmol/L (100 mg/dL) is considered normal; (2) FPG ≥ 5.6 mmol/L (100 mg/dL) but <7.0 mmol/L (126 mg/dL) is defined as IFG; and (3) FPG ≥ 7.0 mmol/L (126 mg/dL) warrants the diagnosis of DM. IFG is comparable to IGT, which is defined as plasma glucose levels between 7.8 and 11.1 mmol/L (140 and 200 mg/dL) 2 h after a 75-g oral glucose load (Table 323-2). Individuals with IFG or IGT are at substantial risk for developing type 2 DM (40% risk over the next 5 years) and cardiovascular disease.

The revised criteria for the diagnosis of DM emphasize the FPG as a reliable and convenient test for diagnosing DM in asymptomatic individuals. A random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is sufficient for the diagnosis of DM (Table 323-2). Oral glucose tolerance testing, although still a valid mechanism for diagnosing DM, is not recommended as part of routine care.

Some investigators have advocated the hemoglobin A1c (A1C) as a diagnostic test for DM. Though there is a strong correlation between elevations in the plasma glucose and the A1C (discussed below), the relationship between the FPG and the A1C in individuals with normal glucose tolerance or mild glucose intolerance is less clear and thus the use of the

A1C is not currently recommended for the diagnosis of diabetes.

The diagnosis of DM has profound implications for an individual from both a medical and financial standpoint. Thus, these diagnostic criteria must be satisfied before assigning the diagnosis of DM. Abnormalities on screening tests for diabetes should be repeated before making a definitive diagnosis of DM, unless acute metabolic derangements or a markedly elevated plasma glucose are present (Table 323-2). The revised criteria also allow for the diagnosis of DM to be withdrawn in situations where the FPG reverts to normal.

SCREENING

Widespread use of the FPG as a screening test for type 2 DM is recommended because: (1) a large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder, (2) epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis, (3) as many as 50% of individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis, and (4) treatment of type 2 DM may favorably alter the natural history of DM. The American Diabetes Association (ADA) recommends screening all individuals >45 years every 3 years and screening individuals with additional risk factors (Table 323-3) at an earlier age. In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM. A number of immunologic markers for type 1 DM are becoming available (discussed below), but their routine use is discouraged pending the identification of clinically beneficial interventions for individuals at high risk for developing type 1 DM.

TABLE 323-3 Risk Factors for Type 2 Diabetes Mellitus

- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Obesity (BMI ≥ 25 kg/m^2)
- Habitual physical inactivity
- Race/ethnicity (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)
- Previously identified IFG or IGT
- History of GDM or delivery of baby >4 kg (>9 lb)
- Hypertension (blood pressure ≥ 140/90 mmHg)
- HDL cholesterol level ≤ 35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome or acanthosis nigracans
- History of vascular disease

Note: BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein.
Source: Adapted from American Diabetes Association, 2004.

INSULIN BIOSYNTHESIS, SECRETION, AND ACTION

BIOSYNTHESIS

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the aminoterminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor (Chap. 317). Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells. Because the C peptide is less susceptible than insulin to hepatic degradation, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia (Chap. 324). Human insulin is now produced by recombinant DNA technology; structural alterations at one or more residues are useful for modifying its physical and pharmacologic characteristics (see below).

SECRETION

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also

influence insulin secretion. Glucose levels >3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by the GLUT2 glucose transporter (Fig. 323-3). Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP-sensitive K^+ channel. This channel consists of two separate proteins: one is the receptor for certain oral hypoglycemics (e.g., sulfonylureas, meglitinides); the other is an inwardly rectifying K^+ channel protein. Inhibition of this K^+ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80 to 150 min. Meals or other major stimuli of insulin secretion induce large (four-

to fivefold increase versus baseline) bursts of insulin secretion that usually last for 2 to 3 h before returning to baseline. Derangements in these normal secretory patterns are one of the earliest signs of beta cell dysfunction in DM.

FIGURE 323-3 Diabetes and abnormalities in glucose-stimulated insulin secretion. Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by the GLUT2 glucose transporter; subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for drugs that act as insulin secretagogues. Mutations in the events or proteins underlined are a cause of maturity onset diabetes of the young (MODY) or other forms of diabetes. SUR, sulfonylurea receptor; ATP, adenosine triphosphate; ADP, adenosine diphosphate. *(Adapted from WL Lowe, in JL Jameson (ed): Principles of Molecular Medicine. Totowa, NJ, Humana, 1998.)*

ACTION

Once insulin is secreted into the portal venous system, ~50% is degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS) (Fig. 323-4). These and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidylinositol-3′-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

FIGURE 323-4 Insulin signal transduction pathway in skeletal muscle. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins.

A number of “docking” proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p65, p110, and phosphatidylinositol-3′-kinase (PI-3-kinase)]. Insulin increases glucose transport through PI-3-kinase and the Cbl pathway, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane. *(Adapted from WL Lowe, in Principles of Molecular Medicine, JL Jameson (ed). Totowa, NJ, Humana, 1998; A Virkamaki et al: J Clin Invest 103:931, 1999. For additional details see* Saltiel and Kahn, 2001.*)*

Glucose homeostasis reflects a precise balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and hormones (e.g., glucagon) result in integrated control of glucose supply and utilization (Chap. 324; see Fig. 324-1). In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis. Glucagon also stimulates glycogenolysis and gluconeogenesis by the liver and renal medulla. Low insulin levels decrease glycogen synthesis, reduce glucose uptake in insulin-sensitive tissues, and promote mobilization of stored precursors. Postprandially, the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes. The major portion of postprandial glucose is utilized by skeletal muscle, an effect of insulin-stimulated glucose uptake. Other tissues, most notably the brain, utilize glucose in an insulin-independent fashion.

PATHOGENESIS

TYPE 1 DM

Type 1A DM develops as a result of the synergistic effects of genetic, environmental, and immunologic factors that ultimately destroy the pancreatic beta cells. The temporal development of type 1A DM is shown schematically as a function of beta cell mass in Fig. 323-5. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. This autoimmune process is thought to be triggered by an infectious or environmental stimulus and to be sustained by a beta cell–specific molecule. In the majority of individuals, immunologic markers appear after the triggering event but before diabetes becomes clinically overt. Beta cell mass then begins to decline, and insulin secretion becomes progressively impaired, although normal glucose tolerance is maintained. The rate of decline in beta cell mass varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until a majority of beta cells are destroyed (~80%). At this point, residual functional beta cells still exist but are insufficient in number to maintain glucose tolerance. The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements, as might occur during infections or puberty. After the initial clinical presentation of type 1A DM, a “honeymoon” phase may ensue during which time glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears

as the autoimmune process destroys the remaining beta cells, and the individual becomes completely insulin deficient.

FIGURE 323-5 Temporal model for development of type 1 diabetes. Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass. The downward slope of the beta cell mass varies among individuals. This progressive impairment in insulin release results in diabetes when ~80% of the beta cell mass is destroyed. A “honeymoon” phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements. *(Adapted from Medical Management of Type 1 Diabetes, 3d ed, JS Skyler (ed). Alexandria, VA, American Diabetes Association, 1998.)*

GENETIC CONSIDERATIONS

Genetic susceptibility to type 1A DM involves multiple genes. The concordance of type 1A DM in identical twins ranges between 30 and 70%, indicating that additional modifying factors must be involved in determining whether diabetes develops. The major susceptibility gene for type 1A DM is located in the HLA region on chromosome 6. Polymorphisms in the HLA complex account for 40 to 50% of the genetic risk of developing type 1A DM. This region contains genes that encode the class II MHC molecules, which present antigen to helper T cells and thus are involved in initiating the immune response (Chap. 296). The ability of class II MHC molecules to present antigen is dependent on the amino acid composition of their antigen-binding sites. Amino acid substitutions may influence the specificity of the immune response by altering the binding affinity of different antigens for class II molecules.

Most individuals with type 1A DM have the HLA DR3 and/or DR4 haplotype. Refinements in genotyping of HLA loci have shown that the haplotypes DQA1*0301, DQB1*0302, DQA1*501, and DQB1*0201 are most strongly associated with type 1A DM. These haplotypes are present in 40% of children with type 1A DM as compared to 2% of the normal U.S. population.

In addition to MHC class II associations, at least 17 different genetic loci contribute susceptibility to type 1A DM. For example, polymorphisms in the promoter region of the insulin gene account for ~10% of the predisposition to type 1A DM. Genes that confer protection against the development of the disease also exist. The haplotype DQA1*0102, DQB1*0602 is present in 20% of the U.S. population but is extremely rare in individuals with type 1A DM (<1%).

The risk of developing type 1A DM is increased tenfold in relatives of individuals with the disease. Nevertheless, most individuals with predisposing haplotypes do not develop diabetes. In addition, most individuals with type 1A DM do not have a first-degree relative with this disorder.

Autoimmune Factors

Although other islet cell types [alpha cells (glucagon-producing), delta cells (somatostatin-producing), or PP cells (pancreatic polypeptide-producing)] are functionally and embryologically similar to beta cells and express most of the same proteins as beta cells, they are inexplicably spared from the autoimmune process. Pathologically, the pancreatic islets are infiltrated with lymphocytes (in a process termed *insulitis*). After all beta cells are destroyed, the inflammatory process abates, the islets become atrophic, and immunologic markers disappear. Studies of the autoimmune process in humans and animal models of type 1A DM (NOD mouse and BB rat) have identified the following abnormalities in both the humoral and cellular arms of the immune system: (1) islet cell autoantibodies; (2) activated lymphocytes in the islets, peripancreatic lymph nodes, and systemic circulation; (3) T lymphocytes that proliferate when stimulated with islet proteins; and (4) release of cytokines within the insulitis. Beta cells seem to be particularly susceptible to the toxic effect of some cytokines [tumor necrosis factor α (TNF-α), interferon γ, and interleukin-1 (IL-1)]. The precise mechanisms of beta cell death are not known but may involve formation of nitric oxide metabolites, apoptosis, and direct CD8+ T cell cytotoxicity. Islet autoantibodies are not thought to be involved in the destructive process, as these antibodies do not generally react with the cell surface of islet cells and are not capable of transferring diabetes mellitus to animals.

Pancreatic islet molecules targeted by the autoimmune process include insulin, glutamic acid decarboxylase (GAD, the biosynthetic enzyme for the neurotransmitter GABA), ICA-512/IA-2 (homology with tyrosine phosphatases), and phogrin (insulin secretory granule protein). Other less clearly defined autoantigens include an islet ganglioside and carboxypeptidase H. With the exception of insulin, none of the autoantigens are beta cell specific, which raises the question of how the beta cells are selectively destroyed. Current theories favor initiation of an autoimmune process directed at one beta cell molecule, which then spreads to other islet molecules as the immune process destroys beta cells and creates a series of secondary autoantigens. The beta cells of individuals who develop type 1A DM do not differ from beta cells of normal individuals, since transplanted islets are destroyed by a recurrence of the autoimmune process of type 1A DM.

Immunologic Markers

Islet cell autoantibodies (ICAs) are a composite of several different antibodies directed at pancreatic islet molecules such as GAD, insulin, IA-2/ICA-512, and an islet ganglioside and serve as a marker of the autoimmune process of type 1A DM. Assays for autoantibodies to GAD-65 are commercially available. Testing for ICAs can be useful in classifying the type of DM as type IA and in identifying nondiabetic individuals at risk for developing type 1A DM. ICAs are present in the majority of individuals (>75%) diagnosed with new-onset type 1A DM, in a significant minority of individuals with newly diagnosed type 2 DM (5 to 10%), and occasionally in individuals with GDM (<5%). ICAs are present in 3 to 4% of first-degree relatives of individuals with type 1A DM. In combination with impaired insulin secretion after intravenous glucose tolerance testing, they predict a >50% risk of developing type 1A DM within 5 years. Without this impairment in insulin secretion, the presence of ICAs predicts a 5-year risk of <25%. Based on these data, the risk of a first-degree relative developing type 1A DM is relatively low. At present, the measurement of ICAs in nondiabetic individuals is a research tool because no treatments have been approved to

prevent the occurrence or progression of type 1A DM.

Environmental Factors

Numerous environmental events have been proposed to trigger the autoimmune process in genetically susceptible individuals; however, none have been conclusively linked to diabetes. Identification of an environmental trigger has been difficult because the event may precede the onset of DM by several years (Fig. 323-5). Putative environmental triggers include viruses (coxsackie and rubella most prominently), bovine milk proteins, and nitrosourea compounds.

Prevention of Type 1A DM

A number of interventions have successfully delayed or prevented diabetes in animal models. Some interventions have targeted the immune system directly (immunosuppression, selective

T cell subset deletion, induction of immunologic tolerance to islet proteins), whereas others have prevented islet cell death by blocking cytotoxic cytokines or increasing islet resistance to the destructive process. Though results in animal models are promising, these interventions have not been successful in preventing type 1A DM in humans. The Diabetes Prevention Trial—type 1 recently concluded that administering insulin to individuals at high risk for developing type 1A DM did not prevent type 1A DM.

TYPE 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although controversy remains regarding the primary defect, most studies support the view that insulin resistance precedes insulin secretory defects and that diabetes develops only if insulin secretion becomes inadequate.

GENETIC CONSIDERATIONS

Type 2 DM has a strong genetic component. Major genes that predispose to this disorder have yet to be identified, but it is clear that the disease is polygenic and multifactorial. Various genetic loci contribute to susceptibility, and environmental factors (such as nutrition and physical activity) further modulate phenotypic expression of the disease. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. Insulin resistance, as demonstrated by reduced glucose utilization in skeletal muscle, is present in many nondiabetic, first-degree relatives of individuals with type 2 DM. However, definition of the genetic susceptibility remains a challenge because the genetic defect in insulin secretion or action may not manifest itself unless an environmental event or another genetic defect, such as obesity, is superimposed. Mutations in various molecules involved in insulin action (e.g., the insulin receptor and enzymes involved in glucose homeostasis) account for a very small fraction of type 2 DM. Likewise, genetic defects

in proteins involved in insulin secretion have not been found in most individuals with type 2 DM. Genome-wide scanning for mutations or polymorphisms associated with type 2 DM is being used in an effort to identify genes associated with type 2 DM. The gene for the protease, calpain 10, is associated with type 2 DM in Hispanic and some other populations.

Pathophysiology

Type 2 DM is characterized by three pathophysiologic abnormalities: impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production. Obesity, particularly visceral or central (as evidenced by the hip-waist ratio), is very common in type 2 DM. Adipocytes secrete a number of biologic products (leptin, TFN-α, free fatty acids, resistin, and adiponectin) that modulate insulin secretion, insulin action, and body weight and may contribute to the insulin resistance. In the early stages of the disorder, glucose tolerance remains normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output (Fig. 323-6). As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue. Markers of inflammation such as IL-6 and C-reactive protein are often elevated in type 2 diabetes.

FIGURE 323-6 Metabolic changes during the development of type 2 diabetes mellitus (DM). Insulin secretion and insulin sensitivity are related, and as an individual becomes more insulin resistant (by moving from point A to point B), insulin secretion increases. A failure to compensate by increasing the insulin secretion results initially in impaired glucose tolerance (IGT; point C) and ultimately in type 2 DM (point D). *(Adapted from SE Kahn, J Clin Endocrinol Metab 86:4047, 2001; RN Bergman, M Ader, Trends Endocrinol Metab 11:351, 2000.)*

Metabolic Abnormalities

INSULIN RESISTANCE

The decreased ability of insulin to act effectively on peripheral target tissues (especially muscle and liver) is a prominent feature of type 2 DM and results from a combination of genetic susceptibility and obesity. Insulin resistance is relative, however, since supernormal levels of circulating insulin will normalize the plasma glucose. Insulin dose-response curves exhibit a rightward shift, indicating reduced sensitivity, and a reduced maximal response, indicating an overall decrease in maximum glucose utilization (30 to 60% lower than normal individuals). Insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output; both effects contribute to the hyperglycemia. Increased hepatic glucose output predominantly accounts for increased FPG levels, whereas decreased peripheral glucose usage results in postprandial hyperglycemia. In skeletal muscle, there is a greater impairment in nonoxidative glucose

usage (glycogen formation) than in oxidative glucose metabolism through glycolysis. Glucose metabolism in insulin-independent tissues is not altered in type 2 DM.

The precise molecular mechanism of insulin resistance in type 2 DM has not been elucidated. Insulin receptor levels and tyrosine kinase activity in skeletal muscle are reduced, but these alterations are most likely secondary to hyperinsulinemia and are not a primary defect. Therefore, postreceptor defects are believed to play the predominant role in insulin resistance (Fig. 323-4). Polymorphisms in IRS-1 may be associated with glucose intolerance, raising the possibility that polymorphisms in various postreceptor molecules may combine to create an insulin-resistant state. The pathogenesis of insulin resistance is currently focused on a PI-3-kinase signaling defect, which reduces translocation of GLUT4 to the plasma membrane, among other abnormalities. Of note, not all insulin signal transduction pathways are resistant to the effects of insulin [e.g., those controlling cell growth and differentiation and using the mitogen-activated protein (MAP) kinase pathway; Fig. 323-4]. Consequently, hyperinsulinemia may increase the insulin action through these pathways, potentially accelerating diabetes-related conditions such as atherosclerosis.

Another emerging theory proposes that elevated levels of free fatty acids, a common feature of obesity, may contribute to the pathogenesis of type 2 DM. Free fatty acids can impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function.

IMPAIRED INSULIN SECRETION

Insulin secretion and sensitivity are interrelated (Fig. 323-6). In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion. The response to other nonglucose secretagogues, such as arginine, is preserved. Eventually, the insulin secretory defect progresses to a state of grossly inadequate insulin secretion.

The reason(s) for the decline in insulin secretory capacity in type 2 DM is unclear. Despite the assumption that a second genetic defect—superimposed upon insulin resistance—leads to beta cell failure, intense genetic investigation has so far excluded mutations in islet

candidate genes. Islet amyloid polypeptide or amylin is cosecreted by the beta cell and likely forms the amyloid fibrillar deposit found in the islets of individuals with long-standing type 2 DM. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment of diabetes may also negatively impact islet function. For example, chronic hyperglycemia paradoxically impairs islet function (“glucose toxicity”) and leads to a worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function. In addition, elevation of free fatty acid levels (“lipotoxicity”) and dietary fat may also worsen islet function.

INCREASED HEPATIC GLUCOSE PRODUCTION

In type 2 DM, insulin resistance in the liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen

storage by the liver in the postprandial state. Increased hepatic glucose production occurs early in the course of diabetes, though likely after the onset of insulin secretory abnormalities and insulin resistance in skeletal muscle.

Insulin Resistance Syndromes

The insulin resistance condition comprises a spectrum of disorders, with hyperglycemia representing one of the most readily diagnosed features. The *metabolic syndrome*, the *insulin resistance syndrome*, or *syndrome X* are terms used to describe a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia [low high-density lipoprotein (HDL) and elevated triglycerides], central or visceral obesity, type 2 diabetes or IGT/IFG, and accelerated cardiovascular disease. This syndrome is very common. The Centers for Disease Control and Prevention (CDC) estimates that 20% of U.S. adults have this syndrome. Epidemiologic evidence supports hyperinsulinemia as a marker for coronary artery disease risk, though an etiologic role has not been demonstrated.

A number of relatively rare forms of severe insulin resistance include features of type 2 DM or IGT (Table 323-1). *Acanthosis nigricans* and signs of hyperandrogenism (hirsutism, acne, and oligomenorrhea in women) are also common physical features. Two distinct syndromes of severe insulin resistance have been described in adults: (1) type A, which affects young women and is characterized by severe hyperinsulinemia, obesity, and features of hyperandrogenism; and (2) type B, which affects middle-aged women and is characterized by severe hyperinsulinemia, features of hyperandrogenism, and autoimmune disorders. Individuals with the type A insulin resistance syndrome have an undefined defect in the insulin-signaling pathway; individuals with the type B insulin resistance syndrome have autoantibodies directed at 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. 326). 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. Both metformin and the thiazolidinediones attenuate hyperinsulinemia, ameliorate hyperandrogenism, induce ovulation, and improve plasma lipids, but they are not approved for this indication.

Prevention

Type 2 DM is preceded by a period of IGT, and a number of life-style modifications and pharmacologic agents prevent or delay the onset of DM. The Diabetes Prevention Program (DPP) demonstrated that intensive changes in life-style (diet and exercise for 30 min/day five times/week) in individuals with IGT prevented or delayed the development of type 2 diabetes 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 life-style intervention group lost 5 to 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; acarbose, metformin, and the thiazolidinediones prevent or delay type 2 DM, but are not approved for this purpose. When administered to nondiabetic individuals for other reasons (cardiac, cholesterol lowering, etc.), two pharmacologic agents (ramipril, pravastatin) reduced the number of new cases of diabetes. Individuals with a strong family history, those at high risk for developing DM, or those with IFG or IGT should be strongly encouraged to maintain a normal body mass index (BMI) and engage in regular physical activity.

GENETICALLY DEFINED, MONOGENIC FORMS OF DIABETES MELLITUS

Several monogenic forms of DM have been identified. Five different variants of MODY, caused by mutations in genes encoding islet cell transcription factors or glucokinase (Fig. 323-3), have been identified so far, and all are transmitted as autosomal dominant disorders (Table 323-1). MODY 2 is the result of mutations in the glucokinase gene that lead to mild-to-moderate hyperglycemia. Glucokinase catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is important for glucose sensing by the beta cells 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. Homozygous mutations in glucokinase cause severe, neonatal diabetes. MODY 1, MODY 3, and MODY 5 are caused by mutations in the hepatocyte nuclear transcription factors (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 (as a result, patients may also have renal absorption abnormalities and renal cysts). The mechanisms by which such mutations lead to DM is not well understood, but it is likely that these factors affect islet development or the transcription of genes that are important in stimulating insulin secretion. MODY 1 and 3 begin with mild hyperglycemia, but progressive impairment of insulin secretion requires treatment with oral agents or insulin. MODY 4 is a rare variant caused by mutations in the insulin promoter factor (IPF) 1, which is a transcription factor that regulates pancreatic development and insulin gene transcription. Homozygous inactivating mutations cause pancreatic agenesis, whereas heterozygous mutations result in DM. Studies of populations with type 2 DM suggest that mutations in the glucokinase gene and various islet cell transcription factors are very rare in ordinary type 2 DM.

ACUTE COMPLICATIONS OF DM

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack immunologic features of type 1A DM and who can subsequently be treated with oral glucose-lowering agents (these individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and HHS are highlighted in Table 323-4. Both disorders are associated with potentially

serious complications if not promptly diagnosed and treated.

TABLE 323-4 Laboratory Values in Diabetic Ketoacidosis (DKA) and Hyperglycemic Hyperosmolar State (HHS) (Representative Ranges at Presentation)

	DKA	***HHS***
Glucose,[a] µmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium,[a]meq/L	Normal to ↑[b]	Normal
Magnesium[a]	Normal[b]	Normal
Chloride[a]	Normal	Normal
Phosphate[a]	↓	Normal
Creatinine, µmol/L (mg/dL)	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/-
Serum bicarbonate,[a] meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial P_{CO_2},[a] mmHg	20–30	Normal
	↑	Normal to slightly ↑

Anion gap[a] [Na - (Cl + HCO_3)], meq/L		

[a]Large changes occur during treatment of DKA.

[b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.

DIABETIC KETOACIDOSIS

Clinical Features

The symptoms and physical signs of DKA are listed in Table 323-5 and usually develop over 24 hours. DKA may be the initial symptom complex that leads to a diagnosis of type 1 DM, but more frequently it occurs in individuals with established diabetes. Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for DKA. Abdominal pain may be severe and can resemble acute pancreatitis or ruptured viscous. Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilation. Kussmaul respirations and a fruity odor on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder. Lethargy and central nervous system depression

may evolve into coma with severe DKA but should also prompt evaluation for other reasons for altered mental status (infection, hypoxia, etc.). Cerebral edema, an extremely serious complication of DKA, is seen most frequently in children. Signs of infection, which may precipitate DKA, should be sought on physical examination, even in the absence of fever. Tissue ischemia (heart, brain) can also be a precipitating factor.

TABLE 323-5 Manifestations of Diabetic Ketoacidosis

Symptoms
Nausea/vomiting

Thirst/polyuria
Abdominal pain
Shortness of breath
Physical findings
Tachycardia
Dry mucous membranes/reduced skin turgor
Dehydration/hypotension
Tachypnea/Kussmaul respirations/respiratory distress
Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen)
Lethargy /obtundation/cerebral edema/possibly coma
Precipitating events
Inadequate insulin administration
Infection (pneumonia/UTI/gastroenteritis/sepsis)
Infarction (cerebral, coronary, mesenteric, peripheral)
Drugs (cocaine)
Pregnancy

Note: UTI, urinary tract infection.

Pathophysiology

DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). Both insulin deficiency and glucagon excess, in particular, are necessary for DKA to develop. The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, as well as increases in substrate delivery from fat and muscle (free fatty acids, amino acids) to the liver.

The combination of insulin deficiency and hyperglycemia reduces the hepatic level of fructose-2,6-phosphate, which alters the activity of phosphofructokinase and fructose-1,6-

bisphosphatase. Glucagon excess decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase. These changes shift the handling of pyruvate toward glucose synthesis and away from glycolysis. The increased levels of glucagon and catecholamines in the face of low insulin levels promote glycogenolysis. Insulin deficiency also reduces levels of the GLUT4 glucose transporter, which impairs glucose uptake into skeletal muscle and fat and reduces intracellular glucose metabolism (Fig. 323-4).

Ketosis results from a marked increase in free fatty acid release from adipocytes, with a resulting shift toward ketone body synthesis in the liver. Reduced insulin levels, in combination with elevations in catecholamines and growth hormone, increase lipolysis and the release of free fatty acids. Normally, these free fatty acids are converted to triglycerides or very low density lipoproteins (VLDL) in the liver. However, in DKA, hyperglucagonemia alters hepatic metabolism to favor ketone body formation, through activation of the enzyme carnitine palmitoyltransferase I. This enzyme is crucial for regulating fatty acid transport into the mitochondria, where beta oxidation and conversion to ketone bodies occur. At physiologic pH, ketone bodies exist as ketoacids, which are neutralized by bicarbonate. As bicarbonate stores are depleted, metabolic acidosis ensues. Increased lactic acid production also contributes to the acidosis. The increased free fatty acids increase triglyceride and VLDL production. VLDL clearance is also reduced because the activity of insulin-sensitive lipoprotein lipase in muscle and fat is decreased. Hypertriglyceridemia may be severe enough to cause pancreatitis.

DKA is initiated by inadequate levels of plasma insulin (Table 323-5). Most commonly, DKA is precipitated by increased insulin requirements, as might occur during a concurrent illness. Failure to augment insulin therapy often compounds the problem. Occasionally, complete omission of insulin by the patient or health care team (in a hospitalized patient with type 1 DM) precipitates DKA. Patients using insulin infusion devices with short-acting insulin are at increased risk of DKA, since even a brief interruption in insulin delivery (e.g., mechanical malfunction) quickly leads to insulin deficiency.

Laboratory Abnormalities and Diagnosis

The timely diagnosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia, ketosis, and metabolic acidosis (increased anion gap) along with a number of secondary metabolic derangements (Table 323-4). Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently <10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total-body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis. Total-body stores of sodium, chloride, phosphorous, and magnesium are also reduced in DKA but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is

not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.

The measured serum sodium is reduced as a consequence of the hyperglycemia [1.6 mmol/L (1.6 meq) reduction in serum sodium for each 5.6 mmol/L (100 mg/dL) rise in the serum glucose]. A normal serum sodium in the setting of DKA indicates a more profound water deficit. In “conventional” units, the calculated serum osmolality [2 × (serum sodium + serum potassium) + plasma glucose (mg/dL)/18 + BUN/2.8] is mildly to moderately elevated, though to a lesser degree than that found in HHS (see below).

In DKA, the ketone body, β-hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, acetoacetate is preferentially detected by a commonly used ketosis detection reagent (nitroprusside). Serum ketones are present at significant levels (usually positive at serum dilution of 1:8 or greater). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril or penicillamine may cause false-positive reactions. Serum or plasma assays for β-hydroxybutyrate more accurately reflect the true ketone body level.

The metabolic derangements of DKA exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings. The degree of acidosis and hyperglycemia do not necessarily correlate closely since a variety of factors determine

the level of hyperglycemia (oral intake, urinary glucose loss). Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia. The differential diagnosis of DKA includes starvation ketosis, alcoholic ketoacidosis (bicarbonate >15 meq/L) and other increased anion gap acidosis (Chap. 42).

TREATMENT

The management of DKA is outlined in Table 323-6. After initiating intravenous fluid replacement and insulin therapy, the agent or event that precipitated the episode of DKA should be sought and aggressively treated. If the patient is vomiting or has altered mental status, a nasogastric tube should be inserted to prevent aspiration of gastric contents. Central to successful treatment of DKA is careful monitoring and frequent reassessment to ensure that the patient and the metabolic derangements are improving. A comprehensive flow sheet should record chronologic changes in vital signs, fluid intake and output, and laboratory values as a function of insulin administered.

TABLE 323-6 Management of Diabetic Ketoacidosis

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH < 7.00 or unconscious.

3. Assess: Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)
   Acid-base status—pH, HCO_3^-, P_{CO_2}, β-hydroxybutyrate
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (5–10 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 250 mg/dL (14 mmol/L).
5. Administer regular insulin: IV (0.1 units/kg) or IM (0.4 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 h. If initial serum potassium is < 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected to > 3.3 mmol/L (3.3.meq/L).
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace K^+: 10 meq/h when plasma K^+ < 5.5 meq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ <3.5 meq/L or if bicarbonate is given.
10. Continue above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

Note: CXR, chest x-ray; ECG, electrocardiogram.
Source: Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 1998; and AE Kitabchi et al: Diabetes Care 24:131, 2001.

After the initial bolus of normal saline, replacement of the sodium and free water deficit is carried out over the next 24 h (fluid deficit is often 3 to 5 L). When hemodynamic stability and adequate urine output are achieved, intravenous fluids should be switched to 0.45% saline at a rate of 200 to 300 mL/h, depending on the calculated volume deficit. The change to 0.45% saline helps to reduce the trend toward hyperchloremia later in the course of DKA. Alternatively, initial use of lactated Ringer's intravenous solution may reduce the hyperchloremia that commonly occurs with normal saline.

A bolus of intravenous (0.15 units/kg) or intramuscular (0.4 units/kg) regular insulin should be administered immediately (Table 323-6), and subsequent treatment should provide continuous and adequate levels of circulating insulin. Intravenous administration is preferred (0.1 units/kg per hour), because it assures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. Intravenous regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.05 to 0.1 units/kg per

hour). Intermediate or long-acting insulin, in combination with subcutaneous regular insulin, should be administered as soon as the patient resumes eating, as this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion until adequate insulin levels are achieved by the subcutaneous route. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse.

Hyperglycemia usually improves at a rate of 4.2 to 5.6 mmol/L (75 to 100 mg/dL) per hour as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. The latter reduces catecholamines, increases urinary glucose loss, and expands the intravascular volume. The decline in the plasma glucose within the first 1 to 2 h may be more rapid and is mostly related to volume expansion. When the plasma glucose reaches 13.9 mmol/L (250 mg/dL), glucose should be added to the 0.45% saline infusion to maintain the plasma glucose in the 11.1 to 13.9 mmol/L (200 to 250 mg/dL) range, and the insulin infusion should be continued. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral ketone body use, suppresses hepatic ketone body formation, and promotes bicarbonate regeneration. However, the acidosis and ketosis resolve more slowly than hyperglycemia. As ketoacidosis improves, β-hydroxybutyrate is converted to acetoacetate. Ketone body levels may appear to increase if measured by laboratory assays that use the nitroprusside reaction, which only detects acetoacetate and acetone. The improvement in acidosis and anion gap, a result of bicarbonate regeneration and decline in ketone bodies, is reflected by a rise in the serum bicarbonate level and the arterial pH. Depending on the rise of serum chloride, the anion gap (but not bicarbonate) will normalize. A hyperchloremic acidosis [serum bicarbonate of 15 to 18 mmol/L (15 to 18 meq/L)] often follows successful treatment and gradually resolves as the kidneys regenerate bicarbonate and excretes chloride.

Potassium stores are depleted in DKA [estimated deficit 3 to 5 mmol/kg (3 to 5 meq/kg)]. During treatment with insulin and fluids, various factors contribute to the development of hypokalemia. These include insulin-mediated potassium transport into cells, resolution of the acidosis (which also promotes potassium entry into cells), and urinary loss of potassium salts of organic acids. Thus, potassium repletion should commence as soon as adequate urine output and a normal serum potassium are documented. If the initial serum potassium level is elevated, then potassium repletion should be delayed until the potassium falls into the normal range. Inclusion of 20 to 40 meq of potassium in each liter of intravenous fluid is reasonable, but additional potassium supplements may also be required. To reduce the amount of chloride administered, potassium phosphate or acetate can be substituted for the chloride salt. The goal is to maintain the serum potassium >3.5 mmol/L (3.5 meq/L). If the initial serum potassium is less than 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is supplemented to >3.3 mmol/L (3.3 meq/L).

Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia. The results of most clinical trials do not support the routine use of bicarbonate replacement, and one study in children found that bicarbonate use was

associated with an increased risk of cerebral edema. However, in the presence of severe acidosis (arterial pH < 7.0 after initial hydration), the ADA advises bicarbonate [50 mmol/L (meq/L) of sodium bicarbonate in 200 mL of 0.45% saline over 1 h if pH = 6.9 to 7.0; or 100 mmol/L (meq/L) of sodium bicarbonate in 400 mL of 0.45% saline over 2 h if pH 7 < 6.9]. Hypophosphatemia may result from increased glucose usage, but randomized clinical trials have not demonstrated

that phosphate replacement is beneficial in DKA. If the serum phosphate is <0.32 mmol/L (1.0 mg/dL), then phosphate supplement should be considered and the serum calcium monitored. Hypomagnesemia may develop during DKA therapy and may also require supplementation.

With appropriate therapy, the mortality of DKA is low (<5%) and is related more to the underlying or precipitating event, such as infection or myocardial infarction. The major nonmetabolic complication of DKA therapy is cerebral edema, which most often develops in children as DKA is resolving. The etiology and optimal therapy for cerebral edema are not well established, but overreplacement of free water should be avoided. Venous thrombosis, upper gastrointestinal bleeding, and acute respiratory distress syndrome occasionally complicate DKA.

Following treatment, the physician and patient should review the sequence of events that led to DKA to prevent future recurrences. Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness. During illness or when oral intake is compromised, patients should: (1) frequently measure the capillary blood glucose; (2) measure urinary ketones when the serum glucose >16.5 mmol/L (300 mg/dL); (3) drink fluids to maintain hydration; (4) continue or increase insulin; and (5) seek medical attention if dehydration, persistent vomiting, or uncontrolled hyperglycemia develop. Using these strategies, early DKA can be prevented or detected and treated appropriately on an outpatient basis.

HYPERGLYCEMIC HYPEROSMOLAR STATE

Clinical Features

The prototypical patient with HHS is an elderly individual with type 2 DM, with a several week history of polyuria, weight loss, and diminished oral intake that culminates in mental confusion, lethargy, or coma. The physical examination reflects profound dehydration and hyperosmolality and reveals hypotension, tachycardia, and altered mental status. Notably absent are symptoms of nausea, vomiting, and abdominal pain and the Kussmaul respirations characteristic of DKA. HHS is often precipitated by a serious, concurrent illness such as myocardial infarction or stroke. Sepsis, pneumonia, and other serious infections are frequent precipitants and should be sought. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder.

Pathophysiology

Relative insulin deficiency and inadequate fluid intake are the underlying causes of HHS. Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle (see above discussion of DKA). Hyperglycemia induces an osmotic diuresis that leads to intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in HHS is not completely understood. Presumably, the insulin deficiency is only relative and less severe than in DKA. Lower levels of counterregulatory hormones and free fatty acids have been found in HHS than in DKA in some studies. It is also possible that the liver is less capable of ketone body synthesis or that the insulin/glucagon ratio does not favor ketogenesis.

Laboratory Abnormalities and Diagnosis

The laboratory features in HHS are summarized in Table 323-4. Most notable are the marked hyperglycemia [plasma glucose may be >55.5 mmol/L (1000 mg/dL)], hyperosmolality (>350 mosmol/L), and prerenal azotemia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased [add 1.6 meq to measured sodium for each 5.6-mmol/L (100 mg/dL) rise in the serum glucose]. In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation.

TREATMENT

Volume depletion and hyperglycemia are prominent features of both HHS and DKA. Consequently, therapy of these disorders shares sev-eral elements (Table 323-6). In both disorders, careful monitoring of the patient's fluid status, laboratory values, and insulin infusion rate is crucial. Underlying or precipitating problems should be aggressively sought and treated. In HHS, fluid losses and dehydration are usually more pronounced than in DKA due to the longer duration of the illness. The patient with HHS is usually older, more likely to have mental status changes, and more likely to have a life-threatening precipitating event with accompanying comorbidities. Even with proper treatment, HHS has a substantially higher mortality than DKA (up to 15% in some clinical series).

Fluid replacement should initially stabilize the hemodynamic status of the patient (1 to 3 L of 0.9% normal saline over the first 2 to 3 h). Because the fluid deficit in HHS is accumulated over a period of days to weeks, the rapidity of reversal of the hyperosmolar state must balance the need for free water repletion with the risk that too rapid a reversal may worsen neurologic function. If the serum sodium is >150 mmol/L (150 meq/L), 0.45% saline should be used. After hemodynamic stability is achieved, the intravenous fluid administration is directed at reversing the free water deficit using hypotonic fluids (0.45% saline initially then 5% dextrose in water, D_5W). The calculated free water deficit (which averages 9 to 10 L) should be reversed over the next 1 to 2 days (infusion rates of 200 to 300 mL/h of hypotonic solution). Potassium repletion is usually necessary and should be dictated by repeated measurements of the serum potassium. In patients taking diuretics, the potassium deficit can be quite large and

may be accompanied by magnesium deficiency. Hypophosphatemia may occur during therapy and can be improved by using KPO_4 and beginning nutrition.

As in DKA, rehydration and volume expansion lower the plasma glucose initially, but insulin is also required. A reasonable regimen for HHS begins with an intravenous insulin bolus of 5 to 10 units followed by intravenous insulin at a constant infusion rate (3 to 7 units/h). As in DKA, glucose should be added to intravenous fluid when the plasma glucose falls to 13.9 mmol/L (250 mg/dL), and the insulin infusion rate should be decreased to 1 to 2 units/h. The insulin infusion should be continued until the patient has resumed eating and can be transferred to a subcutaneous insulin regimen. The patient should be discharged from the hospital on insulin, though some patients can later switch to oral glucose-lowering agents.

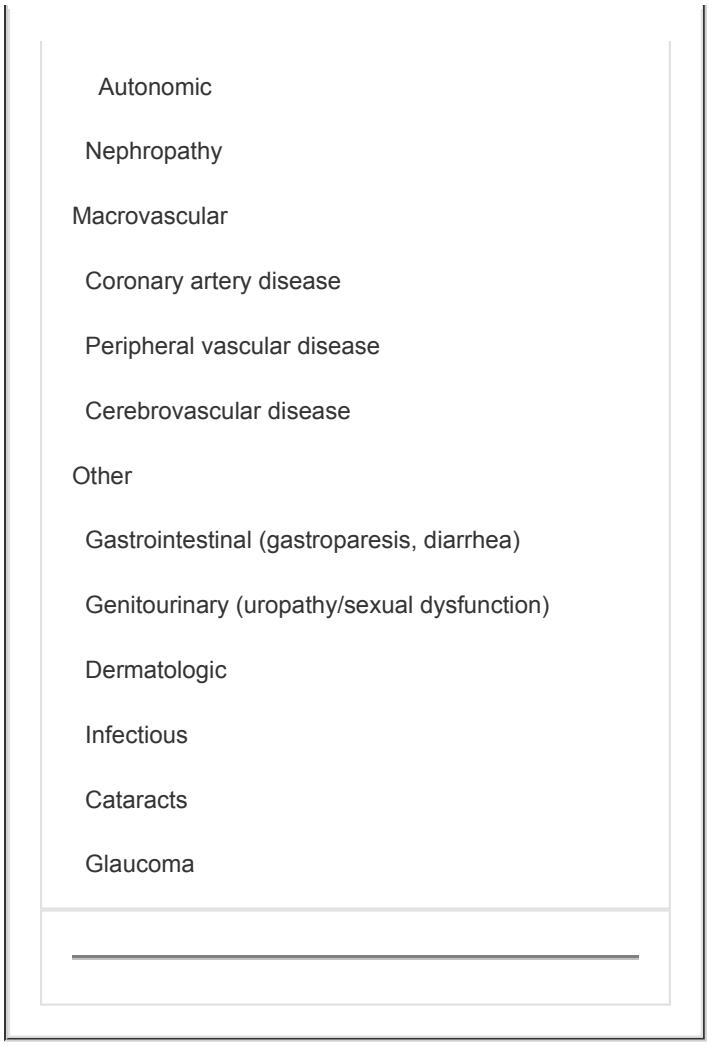
CHRONIC COMPLICATIONS OF DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications (Table 323-7). The vascular complications

of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral arterial disease, cerebrovascular disease). Nonvascular complications include problems such as gastroparesis, infections, and skin changes. The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

TABLE 323-7 Chronic Complications of Diabetes Mellitus

Microvascular
Eye disease
Retinopathy (nonproliferative/proliferative)
Macular edema
Neuropathy
Sensory and motor (mono- and polyneuropathy)



The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Large, randomized clinical trials of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or delays retinopathy, neuropathy, and nephropathy. Other incompletely defined factors may modulate the development of complications. For example, despite long-standing DM, some individuals never develop nephropathy or retinopathy. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications, suggesting that there is a genetic susceptibility for developing particular complications.

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive. However, coronary heart disease events and mortality are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

MECHANISMS OF COMPLICATIONS

Although chronic hyperglycemia is an important etiologic factor leading to complications of DM, the mechanism(s) by which it leads to such diverse cellular and organ dysfunction is unknown. Four prominent theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM (Fig. 323-7).

FIGURE 323-7 Possible molecular mechanisms of diabetes-related complications. AGEs, advanced glycation end products; PKC, protein kinase C; DAG, diacylglycerol; $cPLA_2$, phospholipase A_2; eNOS, endothelial nitric oxide synthase; ROS, reactive oxygen species; Fruc-6-P, fructose-6-phosphate; PAI-1, plasminogen activor inhibitor-1.

One theory is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylaton of intra- and extracellular proteins. Nonenzymatic glycosylation results from the interaction of glucose with amino groups on proteins. AGEs have been shown to cross-link proteins (e.g., collagen, extracellular matrix proteins), accelerate atherosclerosis, promote glomerular dysfunction, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure. The serum level of AGEs correlates with the level of glycemia, and these products accumulate as glomerular filtration rate declines.

A second theory is based on the observation that hyperglycemia increases glucose metabolism via the sorbitol pathway. Intracellular glucose is predominantly metabolized by phosphorylation and subsequent glycolysis, but when increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentration alters redox potential, increases cellular osmolality, generates reactive oxygen species, and likely leads to other types of cellular dysfunction. However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated significant beneficial effects on clinical endpoints of retinopathy, neuropathy, or nephropathy.

A third hypothesis proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PKC). Among other actions, PKC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons.

A fourth theory proposes that hyperglycemia increases the flux through the hexosamine pathway, which generates fructose-6-phosphate, a substrate for O-linked glycosylation and proteoglycan production. The hexosamine pathway may alter function by glycosylation of proteins such as endothelial nitric oxide synthase or by changes in gene expression of transforming growth factor β (TGF-β) or plasminogen activator inhibitor-1 (PAI-1).

Growth factors appear to play an important role in DM-related complications, and their production is increased by most of these proposed pathways. Vascular endothelial growth factor (VEGF) is increased locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. TGF-β is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other

growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may activate all for of the pathways described above. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.

GLYCEMIC CONTROL AND COMPLICATIONS

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM. This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive

diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support. Individuals in the conventional diabetes management group received twice-daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (A1C; 7.3%) than individuals in the conventional diabetes management group (A1C; 9.1%).

The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events. The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from ESRD, and 5.6 years free from lower extremity amputations. If all complications of DM were combined, individuals in the intensive diabetes management group would experience 15.3 more years of life without significant microvascular or neurologic complications of DM, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened.

The benefits of an improvement in glycemic control occurred over the entire range of A1C values (Fig. 323-8), suggesting that at any A1C level, an improvement in glycemic control is beneficial. Therefore, there is no threshold beneath which the A1C can be reduced and the complications of DM prevented. The clinical implication of this finding is that the goal of therapy is to achieve an A1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

FIGURE 323-8 Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different A1C values. *(Adapted from The Diabetes Control and Complications Trial Research Group, Diabetes 44:968, 1995.)*

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This study utilized multiple treatment regimens and monitored the effect of intensive glycemic control and risk factor treatment on the development of diabetic complications. Newly diagnosed individuals with type 2 DM were randomized to (1) intensive management using various combinations of insulin, a sulfonylurea, or metformin; or (2) conventional therapy using dietary modification and pharmacotherapy with the goal of symptom prevention. In addition, individuals were randomly assigned to different antihypertensive regimens. Individuals in the intensive treatment arm achieved an A1C of 7.0%, compared to a 7.9% A1C in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in A1C was associated with a 35% reduction in microvascular complications. As in the DCCT, there was a continuous relationship between glycemic control and development of complications. Improved glycemic control did not conclusively reduce (nor worsen) cardiovascular mortality but was associated with improvement with lipoprotein risk profiles, such as reduced triglycerides and increased HDL.

One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro- and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of DM-related death, stroke, microvascular end points, retinopathy, and heart failure (risk reductions between 32 and 56%). Despite concerns that insulin therapy is associated with weight gain and may worsen underlying insulin resistance and hyperinsulinemia, most available data support strict glycemic control in individuals with type 2 DM.

Similar reductions in the risks of retinopathy and nephropathy were also seen in a small trial of lean Japanese individuals with type 2 DM randomized to either intensive glycemic control or standard therapy with insulin (Kumamoto study). These results demonstrate the effectiveness of improved glycemic control in individuals of different ethnicity, and, presumably a different etiology of DM (i.e., phenotypically different from those in the DCCT and UKPDS).

The findings of the DCCT, UKPDS, and Kumamoto study support the idea that chronic hyperglycemia plays a causative role in the pathogenesis of diabetic microvascular complications. These landmark studies prove the value of metabolic control and emphasize the importance of (1) intensive glycemic control in all forms of DM, and (2) early diagnosis and strict blood pressure control in type 2 DM.

OPHTHALMOLOGIC COMPLICATIONS OF DIABETES MELLITUS

DM is the leading cause of blindness between the ages of 20 and 74 in the United States. The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular edema. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. *Nonproliferative diabetic retinopathy* usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots (Fig. 323-9). Mild nonproliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia.

FIGURE 323-9 Diabetic retinopathy results in scattered hemorrhages and yellow exudates. This patient has neovascular vessels proliferating from the optic disc, requiring urgent pan retinal laser photocoagulation.

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The appearance of neovascularization in response to retinal hypoxia is the hallmark of *proliferative diabetic retinopathy*. These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment. Not all individuals with nonproliferative retinopathy develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy. *Clinically significant macular edema* can occur when only nonproliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years.

Duration of DM and degree of glycemic control are the best predictors of the development of retinopathy; hypertension is also a risk factor. Nonproliferative retinopathy is found in almost all individuals who have had DM for >20 years (25% incidence with 5 years, and 80% incidence with 15 years of type 1 DM). Although there is genetic susceptibility for retinopathy, it confers less influence than either the duration of DM or the degree of glycemic control.

TREATMENT

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 DM. Paradoxically, during the first 6 to 12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term,

improved glycemic control is associated with less diabetic retinopathy. Individuals with known retinopathy are candidates for prophylactic photocoagulation when initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, though adequate ophthalmologic care can prevent most blindness.

Regular, comprehensive eye examinations are essential for all individuals with DM. Most diabetic eye disease can be successfully treated if detected early. Routine, nondilated eye examinations by the primary care provider or diabetes specialist are *inadequate* to detect diabetic eye disease, which requires an ophthalmologist for optimal care of these disorders. Laser photocoagulation is very successful in preserving vision. Proliferative retinopathy is usually treated with panretinal laser photocoagulation, whereas macular edema is treated with focal laser photocoagulation. Although exercise has not been conclusively shown to worsen proliferative diabetic retinopathy, most ophthalmologists advise individuals with advanced diabetic eye disease to limit physical activities associated with repeated Valsalva maneuvers. Aspirin therapy (650 mg/d) does not appear to influence the natural history of diabetic retinopathy, but studies of other antiplatelet agents are under way.

RENAL COMPLICATIONS OF DIABETES MELLITUS

Diabetic nephropathy is the leading cause of ESRD in the United States and a leading cause of DM-related morbidity and mortality. Proteinuria in individuals with DM is associated with markedly reduced survival and increased risk of cardiovascular disease. Individuals with diabetic nephropathy almost always have diabetic retinopathy.

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia (Fig. 323-7). The mechanisms by which chronic hyperglycemia leads to ESRD, though incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperperfusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors. Smoking accelerates the decline in renal function.

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM (Fig. 323-10). Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and cause an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5 to 10 years of type 1 DM, ~40% of individuals begin to excrete small amounts of albumin in the urine. *Microalbuminuria* is defined as 30 to 300 mg/d in a 24-h collection or 30 to 300 μg/mg creatinine in a spot collection (preferred method). The appearance of microalbuminuria (incipient nephropathy) in type 1 DM is an important predictor of progression to overt proteinuria (>300 mg/d) or overt nephropathy. Blood pressure may rise slightly at this point but usually remains in the normal range. Once overt

proteinuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7 to 10 years. The early pathologic changes and albumin excretion abnormalities are reversible with normalization of plasma glucose. However, once overt nephropathy develops, the pathologic changes are likely irreversible.

FIGURE 323-10 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. *(Adapted from RA DeFronzo, in Therapy for Diabetes Mellitus and Related Disorders, American Diabetes Association, Alexandria, VA, 1998.)*

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) microalbuminuria or overt nephropathy may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or overt nephropathy in