HARRISON'S 15TH EDITION

PRINCIPLES OF INTERNAL MEDICINE

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MEDICAL PUBLISHING DIVISION

New York San Francisco Washington, DC Auckland Bogotá Caracas Lisbon London
Madrid Mexico City Milan Montreal New Delhi San Juan Singapore Sydney Tokyo Toronto

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Harrison's
PRINCIPLES OF INTERNAL MEDICINE
Fifteenth Edition

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1234567890 DOWDOW 0987654321
ISBN 0-07-007272-8 (Combo)
0-07-007273-6 (Vol. 1)
0-07-007274-4 (Vol. 2)
0-07-913686-9 (Set)

FOREIGN LANGUAGE EDITIONS

Arabic (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)
Chinese (Twelfth Edition)—McGraw-Hill Book Company—Singapore © 1994
Croatian (Thirteenth Edition)—Placebo, Split, Croatia
French (Fourteenth Edition)—McGraw-Hill Publishing Co., Maidenhead, UK © 1999
German (Fourteenth Edition)—McGraw-Hill Publishing Co., Maidenhead, UK © 1999
Greek (Fourteenth Edition)—Parissianos, Athens, Greece © 2000
Italian (Fourteenth Edition)—McGraw-Hill Libri Italia srl, Milan © 1999
Japanese (Eleventh Edition)—Hirokawa © 1991
Polish (Fourteenth Edition)—Czelej Publishing Company, Lubin, Poland (est. 2000)
Portuguese (Fourteenth Edition)—McGraw-Hill Interamericana do Brasil Ltda © 1998
Romania (Fourteenth Edition)—Teora Publishers, Bucharest, Romania (est. 2000)
Spanish (Fourteenth Edition)—McGraw-Hill Interamericana de Espana, Madrid © 1998
Turkish (Thirteenth Edition)—McGraw-Hill Libri Italia srl (est. 1996)

This book was set in Times Roman by Progressive Information Technologies. The editors were Martin Wonsiewicz and Mariapaz Ramos Englis. The production director was Robert Laffler. The index was prepared by Irving C. Tullar. The text and cover designer was Marsha Cohen/Parallelogram Graphics.

R. R. Donnelley and Sons, Inc. was the printer and binder.

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine—15th ed./editors, Eugene Braunwald . . . [et al.]. p. cm.
Includes bibliographical references and index.
ISBN 0-07-913686-9 (set)—ISBN 0-07-007273-6 (v. 1)—ISBN 0-07-0072744-4 (v. 2)
1. Internal medicine. I. Braunwald, Eugene, date
RC46.H333 2001
616—dc21
00-062800

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third trimester, treatment with adrenergic blocking agents should be undertaken; when the fetus is of sufficient size, cesarean section may be followed by extirpation of the tumor. Although the safety of adrenergic blocking drugs in pregnancy is not established, these agents have been administered in several cases without obvious adverse effect. Antepartum diagnosis and treatment lowers the maternal death rate to that approaching nonpregnant pheochromocytoma patients; fetal death rate, however, remains elevated.

Unresectable and malignant tumors In cases of metastatic or locally invasive tumor in patients with intercurrent illness that precludes surgery, long-term medical management is required. When the manifestations cannot be adequately controlled by adrenergic blocking agents, the concomitant administration of metyrosine may be required. This agent inhibits tyrosine hydroxylase, diminishes catecholamine production by the tumor, and often simplifies chronic management. Malignant pheochromocytoma frequently recurs in the retroperitoneum, and it metastasizes most commonly to bone and lung. Although these malignant tumors are resistant to radiotherapy, combination chemotherapy has had limited success in controlling them. Use of ^{131}I-MIBG has had limited success in the treatment of malignant pheochromocytoma, due to poor uptake of the radioligand.

PROGNOSIS AND FOLLOW-UP The 5-year survival rate after surgery is usually over 95%, the recurrence rate is <10%. After successful surgery, catecholamine excretion returns to normal in about 2 weeks and should be measured to ensure complete tumor removal. Catecholamine excretion should be assessed at the reappearance of suggestive symptoms or yearly if the patient remains asymptomatic. For malignant pheochromocytoma, the 5-year survival rate is <50%.

Complete removal cures the hypertension in approximately three-fourths of patients. In the remainder, hypertension recurs but is usually well controlled by standard antihypertensive agents. In this group, either underlying essential hypertension or irreversible vascular damage induced by catecholamines may cause the persistence of the hypertension.

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Alvin C. Powers

DIABETES MELLITUS

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SPECIAL CONSIDERATIONS IN DIABETES MELLITUS 2135

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 usage, 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, nontraumatic lower extremity amputations, and adult blindness. With an increasing incidence worldwide, DM will likely continue to be a leading cause of morbidity and mortality for the foreseeable future.

CLASSIFICATION

Recent advances in the understanding of the etiology and pathogenesis of diabetes have led to a revised classification (Table 333-1). Although all forms of DM are characterized by hyperglycemia, the pathogenic mechanisms by which hyperglycemia arises differ widely. Some forms of DM are characterized by an absolute insulin deficiency or a genetic defect leading to defective insulin secretion, whereas other forms share insulin resistance as their underlying etiology. Recent changes in classification reflect an effort to classify DM on the basis of the pathogenic process that leads to hyperglycemia, as opposed to criteria such as age of onset or type of therapy (Fig. 333-1).

The two broad categories of DM are designated type 1 and type 2. Type 1A DM results from autoimmune beta cell destruction, which usually leads to insulin deficiency. Type 1B DM is also characterized by insulin deficiency as well as a tendency to develop ketosis. However, individuals with type 1B DM lack immunologic markers indicative of an autoimmune destructive process of the beta cells. The mechanisms leading to beta cell destruction in these patients are unknown. Relatively few patients with type 1 DM fall into the type 1B idiopathic category; many of these individuals are either African-American or Asian in heritage.

Type 2 DM is a heterogeneous group of disorders usually 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). The identification of distinct pathogenic processes in type 2 DM has important potential therapeutic implications, as pharmacologic agents that target specific metabolic derangements become available.

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)

Table 333-1 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. Mitochondrial DNA
    - 7. Proinsulin or insulin conversion
  - B. Genetic defects in insulin action
    - 1. Type A insulin resistance
    - 2. Leprechaunism
    - 3. Rabson-Mendenhall syndrome
    - 4. Lipoatrophic diabetes
  - 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, 2000

are obsolete. These previous designations reflected the observation that most individuals with type 1 DM (previously IDDM) have an absolute requirement for insulin treatment, whereas many individuals with type 2 DM (previously NIDDM) do not require insulin therapy to prevent ketoacidosis. However, because many individuals with type 2 DM eventually require insulin treatment for control of glycemia, the use of the latter term generated considerable confusion.

A second difference is that age is no longer used as a criterion in the new 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. In fact, it is estimated that between 5 and 10% of individuals who develop DM after age 30 have type 1A DM. Likewise, although type 2 DM more typically develops with increasing age, 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, and a host of conditions that impair glucose tolerance (Table 333-1). *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. Several endocrinopathies can lead to DM as a result of excessive secretion of hormones that antagonize the action of insulin. Notable within this group are acromegaly and Cushing's disease, both of which may present with DM. 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 and first become recognized during pregnancy. Insulin resistance related to the metabolic changes of late pregnancy increases insulin requirements and may lead to hyperglycemia or impaired glucose tolerance. GDM is seen 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. It is projected that the number of individuals with DM will continue to increase in the near future. Between 1976 and 1994, for example, the prevalence of DM among adults in the United States increased from 8.9% to 12.3%. These findings, based on national epidemiologic data, include individuals with a diagnosis of DM and those with undiagnosed DM (based on identical diagnostic criteria). Likewise, prevalence rates of impaired fasting glucose (IFG) increased from 6.5% to 9.7% over the same period. 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.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. For example, Scandinavia has the highest rate of type 1 DM (in Finland, incidence is 35/100,000 per year). The

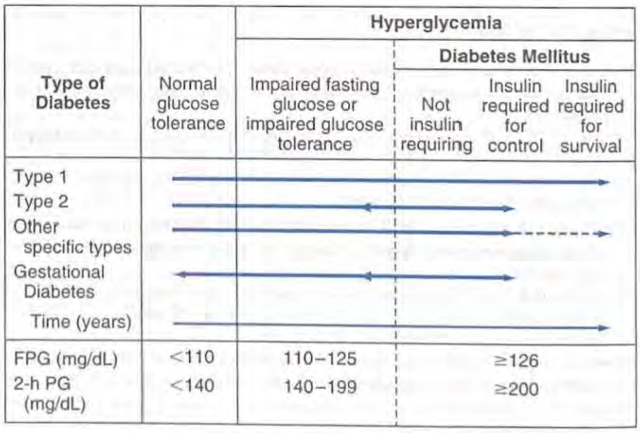

FIGURE 333-1 Spectrum of glucose homeostasis and diabetes. The spectrum from normal glucose tolerance to diabetes in type 1 diabetes, type 2 diabetes, other specific types of diabetes, and gestational diabetes is shown from left to right. In most types of diabetes, the individual traverses from normal glucose tolerance to impaired glucose tolerance to frank diabetes. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes. For example, individuals with type 2 diabetes may return to the impaired glucose tolerance category with weight loss; in gestational diabetes, 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 (as defined by recent consensus panels—see text). These values do not apply to the diagnosis of gestational diabetes. Some types of diabetes may or may not require insulin for survival, hence the dotted line. (Conventional units are used in the figure.) *(Adapted from American Diabetes Association: Clinical Practice Guidelines, 2000)*

Pacific Rim has a much lower rate (in Japan and China, 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, impaired glucose tolerance (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 both genetic and environmental factors. There is also considerable variation in DM prevalence among different ethnic populations within a given country.

In 1998, approximately 16 million individuals in the United States met the diagnostic criteria for DM. This represents ~6% of the population. About 800,000 individuals in the United States develop DM each year. The vast majority of these (>90%) have type 2 DM. The number of people with DM increases with the age of the population, ranging from an incidence of ~1.5% in individuals from 20 to 39 years to ~20% of individuals >75 years. The incidence of DM is similar in men and women throughout most age ranges but is slightly greater in men >60 years. The prevalence of DM is approximately twofold greater in African Americans, Hispanic Americans, and Native Americans than in non-Hispanic whites, and the onset of type 2 DM occurs, on average, at an earlier age in the former groups than in the non-Hispanic white population. The incidence of type 2 DM in these ethnic groups is rapidly increasing. The reasons for these differences are not yet clear.

DIAGNOSIS

Revised criteria for diagnosing DM have been issued by consensus panels of experts from the National Diabetes Data Group and the World Health Organization (Table 333-2). The revised criteria reflect new epidemiologic and metabolic evidence and are based on the following premises: (1) the spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load varies in normal individuals, and (2) DM defined as the level of glycemia at which diabetes-specific complications are noted and not on the level of glucose tolerance from a population-based viewpoint. 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. 333-2).

Glucose tolerance is classified into three categories based on the FPG: (1) FPG < 6.1 mmol/L (110 mg/dL) is considered normal; (2) FPG ≥ 6.1 mmol/L (110 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 a new diagnostic category defined by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. It is analogous 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 333-2). Individuals with IFG or IGT are at substantial risk for developing type 2 DM and cardiovascular disease in the future, though they may not meet the criteria for DM.

Table 333-2 Criteria for the Diagnosis of Diabetes Mellitus

- Symptoms of diabetes plus random blood glucose concentration ≥11.1 mmol/L (200 mg/dL)[a]

or

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL)[b]

or

- Two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test[c]

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

[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.

SOURCE: Adapted from American Diabetes Association, 2000.

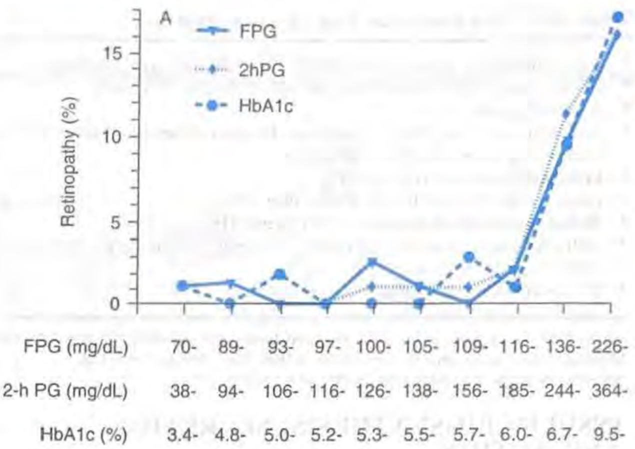

FIGURE 333-2 Relationship of diabetes-specific complication and glucose tolerance. This figure shows the incidence of retinopathy in Pima Indians as a function of the fasting plasma glucose (FPG), the 2-h plasma glucose after a 75-g oral glucose challenge (2hPG), or glycated hemoglobin (HbA1c). Note 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 HbA1c >6.0%. (Conventional units are used in the figure.) *(From American Diabetes Association: Clinical Practice Guidelines, 2000, as adapted from McCance et al: BMJ 308:1323, 1994)*

The revised criteria for the diagnosis of DM emphasize the FPG as the most 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 333-2). Oral glucose tolerance testing, although still a valid mechanism for diagnosing DM, is not recommended as part of routine screening.

Some investigators have advocated the hemoglobin A1c (HbA1c) as a diagnostic test for DM. Though there is a strong correlation between elevations in the plasma glucose and the HbA1c (discussed below), the relationship between the FPG and the HbA1c in individuals with normal glucose tolerance or mild glucose intolerance is less clear, and the test is not universally standardized or available.

The diagnosis of DM has profound implications for an individual from both a medical and financial standpoint. Thus, the health care provider must be certain that these criteria are completely satisfied before assigning the diagnosis of DM to an individual. The revised criteria also allow for the diagnosis of DM to be withdrawn in situations where the FPG no longer exceeds these criteria. 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 333-2).

SCREENING Widespread use of the FPG as a screening test for type 2 DM is strongly encouraged because: (1) a large number of individuals who meet the current criteria for DM are unaware that they have the disorder, (2) epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis, and (3) as many as 50% of individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis. The Expert Committee suggests screening all individuals >45 years every 3 years and screening asymptomatic individuals with additional risk factors (Table 333-3) at an earlier age. In contrast to type 2 DM, it is rare for an individual to have a long asymptomatic period of hyperglycemia prior to the diagnosis of type 1 DM. A number of immunologic markers for type 1 DM are becoming available (discussed below), but their use is currently discouraged pending the identification of clinically beneficial interventions for individuals at high risk for developing type 1 DM.

Table 333-3 Risk Factors for Type 2 Diabetes Mellitus

- Family history of diabetes (i.e., parent or sibling with type 2 diabetes)
- Obesity (i.e., ≥20% desired body weight or BMI ≥ 27 kg/m²)
- Age ≥45 years
- 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 over 9 lbs
- Hypertension (blood pressure ≥ 140/90 mm Hg)
- HDL cholesterol level ≤0.90 mmol/L (35 mg/dL) and/or a triglyceride level ≥2.82 mmol/L (250 mg/dL)
- Polycystic ovary syndrome

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, 2000.

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. 327). 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 a marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia (Chap. 334). 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, as well as inducing insulin secretion. Glucose stimulates insulin secretion through a series of regulatory steps that begin with transport into the beta cell by the GLUT2 glucose transporter (Fig. 333-3). 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 is a complex of two separate proteins, one of which is the receptor for certain oral hypoglycemics (e.g., sulfonylureas, meglitinides); the other subunit is an inwardly rectifying K⁺ channel protein. Inhibition of this K⁺ channel induces beta cell membrane depolarization, opening of voltage-dependent calcium channels (leading to an influx of calcium), and stimulation of insulin secretion. Careful studies of insulin secretory profiles reveal 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 (see below).

ACTION Once insulin is secreted into the portal vein, ~50% is removed and degraded by the liver. Unextracted insulin enters the systemic circulation and binds to its receptor in target sites. The insulin receptor belongs to the tyrosine kinase class of membrane-bound receptors (Chap. 327). Insulin binding to the receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS) 1 and 2 (Fig. 333-4). These and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, ultimately 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.

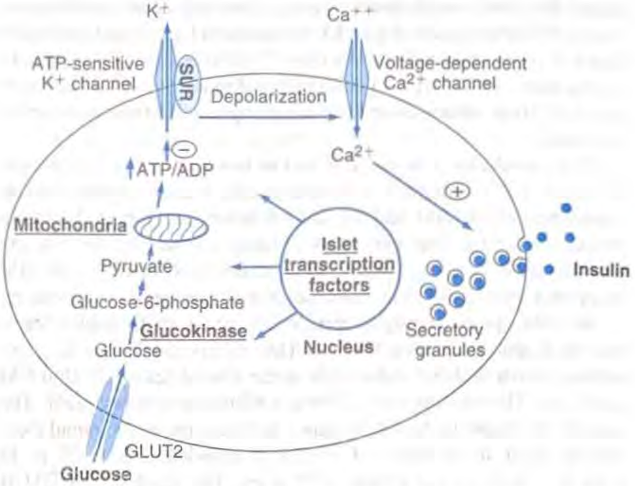

FIGURE 333-3 Diabetes and abnormalities in glucose-stimulated insulin secretion. Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by the GLUT2 glucose transporter; subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for oral hypoglycemic agents. 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 Lowe, 1998.)*

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 the effects of other pathways including neural input, metabolic signals, and hormones (e.g., glucagon) result in integrated control of glucose supply and utilization (Chap. 334; Fig. 334-1). In the fasting state, low insulin levels promote hepatic gluconeogenesis and glycogenolysis to prevent hypoglycemia. Low insulin levels decrease glycogen synthesis, reduce glucose uptake in insulin-sensitive tissues, and promote mobilization of stored precursors. Reduced insulin levels are also permissive in allowing glucagon to stimulate glycogenolysis and gluconeogenesis by the liver and renal medulla. These processes are of critical importance to ensure an adequate glucose supply for the brain. Postprandially, a large 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. 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. 333-5. 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. Following 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.

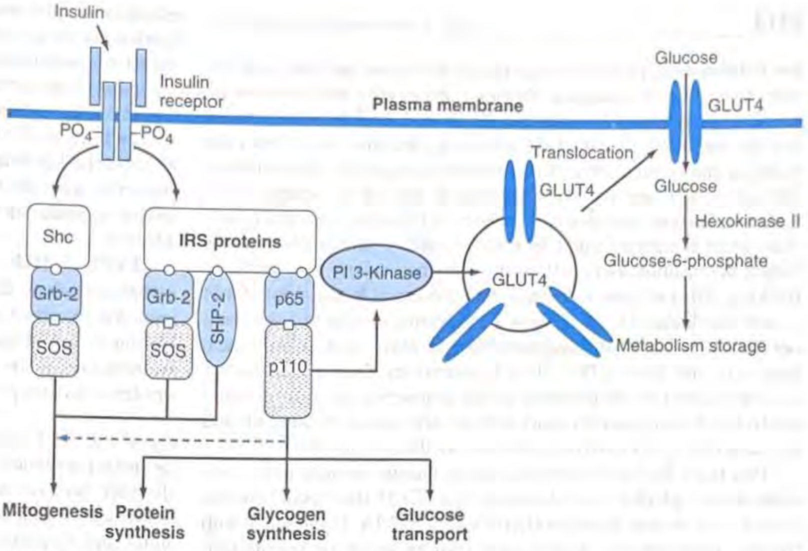

FIGURE 333-4 Insulin signal transduction pathway. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of "docking" proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p65, p110, and phosphoinositol phosphate 3-kinase (PI 3-kinase)]. Insulin increases glucose transport through PI 3-kinase, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane. *(Adapted from Lowe, 1998; Virkamaki et al, 1999)*

GENETIC CONSIDERATIONS The genetic contributions to type 1A DM involve multiple genes. The development of the disease appears to require inheritance of a sufficient complement of genes to confer susceptibility to the disorder. 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 appear to 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 (Chaps. 305, 306, 307). 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 the 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 and DQA1*501, DQB1*0201 have the strongest association 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 may contribute susceptibility to type 1A DM. For example, polymorphisms in the promoter region of the insulin gene appear to account for ~10% of the predisposition to type 1A DM. Genes that confer protection against the development of the disease also exist. For example, 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%).

Although type 1A DM is clearly associated with certain predisposing genotypes, most individuals with these haplotypes do not develop diabetes. In addition, most individuals with type 1A DM do not have a first-degree relative with this disorder. Nevertheless, the risk of developing type 1A DM for relatives of individuals with the disease is considerably higher compared to the risk for the general population. ■

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,

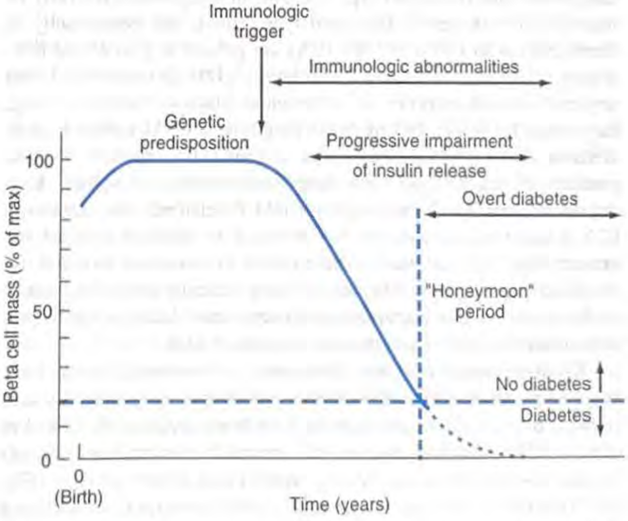

FIGURE 333-5 Temporal model for development of type 1 diabetes. Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass. The downward slope of the beta cell mass varies among individuals. This 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)*

the inflammatory process abates, the islets become atrophic, and immunologic markers disappear. Studies of the insulitis and 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, interferon γ, and interleukin 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/ICA512, and an islet ganglioside and serve as a marker of the autoimmune process of type 1A DM. Testing for ICAs can be useful in classifying the type of DM as type 1A 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, 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 conjunction with impaired insulin secretion on 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, and even ICA-positive individuals are not destined to develop diabetes. At present, the ICAs are used predominantly as a research tool and not in clinical practice, in part because of the technically demanding nature of the assay but also because no treatments have been proven 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. 333-5). Putative environmental triggers include viruses (coxsackie and rubella most prominently), early exposure to bovine milk proteins, and nitrosourea compounds. Epidemiologic studies have noted an association between bovine milk intake and type 1A DM; studies are ongoing to investigate a possible relationship between exposure to bovine milk and the autoimmune process of type 1A DM.

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, most of these interventions have not been successful in preventing type 1A DM in humans. Clinical trials of several interventions are underway in the United States and Europe. The Diabetes Prevention Trial—type 1 is being conducted to determine whether administering insulin to individuals at high risk for developing type 1A DM can induce immune tolerance and alter the autoimmune process of type 1A DM.

TYPE 2 DM Type 2 DM is a heterogeneous disorder with a complex etiology that develops in response to genetic and environmental influences. Central to the development of type 2 DM are insulin resistance and abnormal insulin secretion. Although controversy remains regarding the primary defect, most studies support the view that insulin resistance precedes insulin secretory defects.

GENETIC CONSIDERATIONS Type 2 DM has a strong genetic component. Although the major genes that predispose to this disorder have yet to be identified, 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 in offspring may reach 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 abnormalities of type 2 DM 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.

The identification of individuals with mutations in various molecules involved in insulin action (e.g., the insulin receptor and enzymes involved in glucose homeostasis) has been useful for characterizing key steps in insulin action. However, mutations in these molecules 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. ■

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, is very common in type 2 DM. Insulin resistance associated with obesity augments the genetically determined insulin resistance of type 2 DM. Adipocytes secrete a number of biologic products (leptin, tumor necrosis factor α, free fatty acids) that modulate processes such as 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. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets become unable to sustain the hyperinsulinemic state. IGT, marked 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.

Metabolic Abnormalities • ***Insulin resistance*** This is caused by the decreased ability of insulin to act effectively on peripheral target tissues (especially muscle and liver) and is a prominent feature of type 2 DM. This resistance is relative, 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). Resistance to the action of insulin impairs glucose utilization by insulin-sensitive tissues and increases hepatic glucose output—both effects contributing to the hyperglycemia of diabetes. 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 usage in insulin-independent tissues is not decreased in type 2 DM.

The precise molecular mechanism of insulin resistance in type 2 DM has yet to be 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. 333-4). 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.

A current focus for the pathogenesis of insulin resistance focuses on a PI-3 kinase signaling defect, which causes reduced 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). Consequently, hyperinsulinemia may actually increase the insulin action through these pathways.

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 in several different ways. 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. 333-6). In type 2 DM, insulin secretion initially increases in response to insulin resistance in order 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. Some endogenous insulin production continues, but the amount secreted is less than the amount secreted by normal individuals at the same plasma glucose concentration.

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 longstanding type 2 DM. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment may also impact islet function negatively. 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") also worsens islet function.

Increased hepatic glucose production The liver maintains plasma glucose during periods of fasting through glycogenolysis and gluconeogenesis using substrates derived from skeletal muscle and fat (alanine, lactate, glycerol, and fatty acids). Insulin promotes the storage of glucose as hepatic glycogen and suppresses gluconeogenesis. In type 2 DM, insulin resistance in the liver arises from the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glucose 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 It is likely that the insulin resistance condition comprises a spectrum of disorders, with hyperglycemia representing one of the most readily diagnosed features. *Syndrome X* is a term used to describe a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia, central or visceral obesity, endothelial dysfunction, and accelerated cardiovascular disease. Epidemiologic evidence supports hyperinsulinemia as a marker for coronary artery disease risk, though an etiologic role has not been demonstrated.

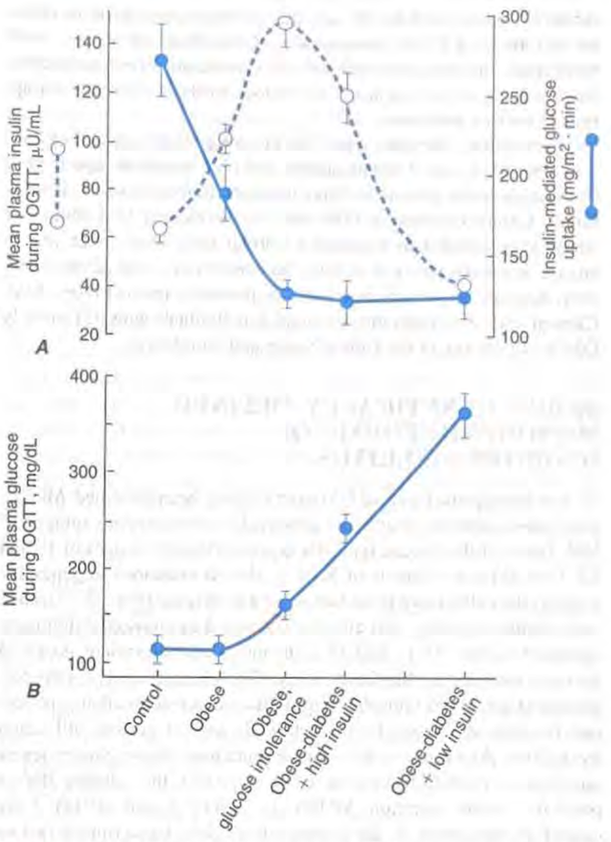

FIGURE 333-6 Metabolic changes during the development of type 2 diabetes. *A*. The mean plasma insulin and insulin-mediated glucose uptake during an oral glucose tolerance test (OGTT). *B*. The mean plasma glucose during an OGTT. On the x-axis are groups of: control individuals, obese individuals, obese and glucose intolerant individuals, obese individuals with diabetes and high insulin, and obese individuals with diabetes and low insulin. *(From RA DeFronzo: Lilly lecture. The triumvirate: Beta-cell, muscle, liver: A collusion responsible for NIDDM. Diabetes 37:667, 1998, with permission.)*

A number of forms of severe insulin resistance may be associated with a phenotype similar to that in type 2 DM or IGT (Table 333-1). *Acanthosis nigricans* and signs of hyperandrogenism (hirsutism, acne, and oligomenorrhea) are common physical features. In addition to rare genetic syndromes seen in early childhood, 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. 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 thiazolidinediones may attenuate hyperinsulinemia, ameliorate hyperandrogenism, and induce ovulation, but are not approved for this indication.

Prevention Because type 2 DM is preceded by a period of IGT, a number of life-style modifications and pharmacologic agents have been suggested to prevent or delay its onset. Individuals with a strong family history or those at high risk for developing DM should be strongly encouraged to maintain a normal body mass index and to engage in regular physical activity. Beyond this general advice, however, there are no specific interventions proven to prevent type 2 DM. Clinical trials of various interventions in individuals with IGT or early DM are underway in the United States and worldwide.

MODY: GENETICALLY DEFINED, MONOGENIC FORMS OF DIABETES MELLITUS

Several monogenic forms of DM have recently been identified. MODY comprises a phenotypically and genetically heterogeneous subtype of DM. Onset of the disease typically occurs between the ages of 10 and 25. Five different variants of MODY, due to mutations in genes encoding islet cell transcription factors or glucokinase (Fig. 333-3), have been identified so far, and all are transmitted as autosomal dominant disorders (Table 333-1). MODY 2, the most common variant, is caused by mutations in the glucokinase gene. 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. 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. 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 4 is a rare variant caused by mutations in the insulin promoter factor (IPF-1), which is a transcription factor that regulates both pancreatic development and insulin gene transcription. Homozygous inactivating mutations lead to pancreatic agenesis, whereas heterozygous mutations result in early-onset DM. Studies of populations with type 2 DM suggest that mutations in the glucokinase gene and various islet cell transcription factors do not account for ordinary type 2 DM. Nevertheless, elucidation of the molecular genetics underlying these rare forms of DM has been important in identifying critical steps in the control of pancreatic beta cell function.

Table 333-4 Laboratory Values in Diabetic Ketoacidosis (DKA) and Nonketotic Hyperosmolar States (NKHS) (Representative Ranges at Presentation)

	DKA	NKHS
Glucose,[a] mmol/L (mg/dL)	16.7–33.3 (300–600)	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}, mmHg	20–30	Normal
Anion gap[a] [Na − (Cl + HCO_3)], meq/L	↑	Normal to slightly ↑

[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.

COMPLICATIONS OF DM

ACUTE COMPLICATIONS Diabetic ketoacidosis (DKA) and nonketotic hyperosmolar state (NKHS) are acute complications of diabetes. DKA is seen primarily in individuals with type 1 DM, and NKHS is seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental status. DKA and NKHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and NKHS are highlighted in Table 333-4. Both disorders are associated with potentially serious complications if not promptly diagnosed and treated.

DIABETIC KETOACIDOSIS **Clinical Features** The symptoms and physical signs of DKA are listed in Table 333-5. 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 sometimes suggests acute pancreatitis or ruptured viscous. Hyperglycemia leads to glucosuria, volume depletion, tachycardia, and possibly hypotension. Kussmaul respirations and an acetone odor on the patient's breath (both secondary to metabolic acidosis) are classic signs of the disorder. Lethargy and central nervous system depression may evolve into coma with severe DKA. 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.

Pathophysiology DKA results from 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 hyperglycemia of DKA results from increased hepatic glucose production (gluconeogenesis and glycogenolysis) and impaired peripheral glucose utilization. The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver, as well as increasing 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 hepatic changes shift the handling of pyruvate toward glucose synthesis and away from glycolysis. Glycogenolysis is promoted by the increased levels of glucagon and catecholamines in the face of low insulin levels. 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. 333-4).

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, lead to an increase in lipolysis and release of free fatty acids. Normally, these free fatty acids are converted to triglycerides or very low density lipoproteins (VLDL) in the liver, but 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

Table 333-5 Manifestations of Diabetic Ketoacidosis

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

NOTE: UTI, urinary tract infection.

the mitochondria, where beta oxidation and conversion to ketone bodies occurs. 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 result in increased triglyceride production and increased hepatic production of VLDL. VLDL clearance is also reduced because the activity of insulin-sensitive lipoprotein lipase is decreased. Hypertriglyceridemia may be severe enough to cause pancreatitis.

DKA can be precipitated by inadequate levels of plasma insulin for a variety of reasons (Table 333-5). Most commonly, DKA is precipitated when relatively insufficient insulin is available when insulin requirements increase, as might occur during a concurrent illness. Failure to augment insulin therapy appropriately by the patient or health care team 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 have a greater potential for 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 333-4)). 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 is typically at the high end of the normal range or 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. 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.

The measured serum sodium is reduced as a consequence of the hyperglycemia [1.6 meq (1.6 mmol/L) reduction in serum sodium for each 100 mg/dL (5.6 mmol/L) 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 NKHS hyperosmolar state (see below).

In DKA, the ketone body, β-hydroxybutyrate, is synthesized at a threefold greater rate than acetoacetate; however, the latter ketone body 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, as 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.

℞ **TREATMENT** The management of DKA is outlined in Table 333-6. 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 patient 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.

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 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 or intramuscular insulin (10 to 20 units) should be administered immediately (Table 333-6)), and subsequent treatment should provide continuous and adequate levels of circulating insulin. Intravenous administration is preferred, because it assures

Table 333-6 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}
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L 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 14 mmol/L (250 mg/dL).
5. Administer regular insulin: 10–20 units IV or IM, then 5–10 units/h by continuous IV infusion; increase 2- to 10-fold if no response by 2–4 h.
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event [cultures, chest x-ray, electrocardiogram (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 8.3–13.9 mmol/L (150–250 mg/dL), until acidosis is resolved. Insulin infusion may be decreased to 1–4 units/h.
11. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

SOURCE: Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, 1998.

rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. Intravenous 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 1 to 4 units/h). 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 allow for 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 at a slower rate than does the 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 levels. 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 is minimized by the use of hypotonic intravenous solutions. This gradually resolves as the kidney regenerates bicarbonate and excretes chloride.

Potassium stores are depleted in DKA [estimated deficit 3 to 5 mmol/kg (3 to 5 meq/kg)], but the serum potassium may be normal or even elevated at the time of presentation. 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).

Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary or advisable. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, impair tissue oxygenation, and promote hypokalemia. The results of most clinical trials do not support the routine use of bicarbonate replacement. In the presence of severe acidosis (arterial pH $<$ 7.0 or hypotension unresponsive to fluid resuscitation), some physicians administer bicarbonate [50 to 150 mmol/L (meq/L) of sodium bicarbonate in 250 mL of 0.45% saline over 1 to 2 h until the serum bicarbonate rises to approximately 10 mmol/L (meq/L)]. 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 and adult respiratory distress syndrome occasionally complicate DKA.

Following successful treatment of DKA, 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. In this way, early DKA can be detected and treated appropriately on an outpatient basis.

NONKETOTIC HYPEROSMOLAR STATE **Clinical Features** NKHS is most commonly seen in elderly individuals with type 2 DM. Its most prominent features include polyuria; orthostatic hypotension; and a variety of neurologic symptoms that include altered mental status, lethargy, obtundation, seizure, and possibly coma. The prototypical patient is a mildly diabetic, elderly individual 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. NKHS 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 thoroughly. In addition, a debilitating condition (prior stroke or dementia) or social situation that compromises water intake may contribute to the development of the disorder. Finally, the development of NKHS can be associated with the use of certain medications (thiazide diuretics, glucocorticoids, phenytoin).

Pathophysiology Insulin deficiency and inadequate fluid intake are the underlying causes of NKHS. Insulin deficiency increases hepatic glucose production (through glycogenolysis and gluconeogenesis) and impairs glucose utilization in skeletal muscle (see above discussion under DKA). Hyperglycemia induces an osmotic diuresis that leads to profound intravascular volume depletion, which is exacerbated by inadequate fluid replacement. The absence of ketosis in NKHS 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 NKHS 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 NKHS are summarized in Table 333-4. 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 NKHS and DKA. Consequently, therapy of these disorders involves several shared elements (Table 333-6). 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 NKHS, the volume depletion, free water deficit, and hyperosmolality are greater than in DKA. The patient with NKHS is usually older, more likely to have mental status changes, and thus more likely to have a life-threatening precipitating event with accompanying comorbidities. Even with proper treatment, NKHS has a substantially higher mortality than DKA (up to 50% 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 NKHS 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 and the observation that too rapid a reversal may worsen neurologic function. If the serum sodium is >150mmol/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 eventually required. In NKHS, patients tend to be more sensitive to insulin than in DKA and dose requirements are not usually as large. A reasonable regimen for NKHS 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 undergo a trial of oral glucose-lowering agents.

CHRONIC COMPLICATIONS 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 333-7). The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, cerebrovascular disease). Nonvascular complications include problems such as gastroparesis, sexual dysfunction, and skin changes. This division is rather arbitrary since it is likely that multiple pathogenic processes are involved in all forms of complications.

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 may have a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

The microvascular complications of both type 1 and type 2 DM result from chronic hyperglycemia. Randomized, prospective clinical trials involving large numbers of individuals with type 1 or type 2 DM have conclusively demonstrated that a reduction in chronic hyperglycemia prevents or reduces retinopathy, neuropathy, and nephropathy. Other incompletely defined factors also modulate the development of complications. For example, despite longstanding DM, some individuals never develop nephropathy or retinopathy. Many of these patients have glycemic control that is indistinguishable from those who develop microvascular complications. Because of these observations, it is suspected that a genetic susceptibility for developing particular complications exists. However, the genetic loci responsible for these susceptibilities have not yet been identified.

Table 333-7 Chronic Complications of Diabetes Mellitus

- Microvascular
  - Eye disease
    - Retinopathy (nonproliferative/proliferative)
    - Macular edema
    - Cataracts
    - Glaucoma
  - Neuropathy
    - Sensory and motor (mono- and polyneuropathy)
    - Autonomic
  - Nephropathy
- Macrovascular
  - Coronary artery disease
  - Peripheral vascular disease
  - Cerebrovascular disease
- Other
  - Gastrointestinal (gastroparesis, diarrhea)
  - Genitourinary (uropathy/sexual dysfunction)
  - Dermatologic

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive, but some results suggest a role for chronic hyperglycemia in the development of macrovascular disease. For example, 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 HbA1c. 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. Three major theories, which are not mutually exclusive, have been proposed to explain how hyperglycemia might lead to the chronic complications of DM (Fig. 333-7).

One hypothesis is that increased intracellular glucose leads to the formation of advanced glycosylation end products (AGEs) via the nonenzymatic glycosylaton of cellular 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 hypothesis proposed to explain how chronic hyperglycemia leads to complications of DM 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 intracellular glucose is increased, some glucose is converted to sorbitol by the enzyme aldose reductase. Increased sorbitol concentrations affect several aspects of cellular physiology (decreased myoinositol, altered redox potential) and may lead to cellular dysfunction. However, testing of this theory in humans, using aldose reductase inhibitors, has not demonstrated 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 certain isoforms of protein kinase C (PKC), which, in turn, affect a variety of cellular events that lead to DM-related complications. For example, PKC activation by glucose alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons in vitro. Growth factors appear to play an important role in DM-related complications. Vascular endothelial growth factor (VEGF) is increased locally in diabetic proliferative ret-

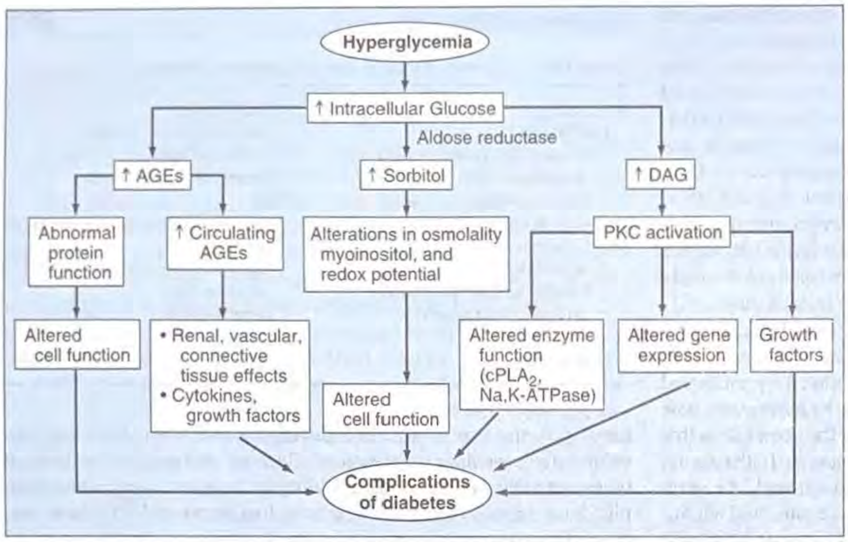
Hyperglycemia
↑ Intracellular Glucose
Aldose reductase
↑ AGEs
↑ Sorbitol
↑ DAG
Abnormal protein function
↑ Circulating AGEs
Alterations in osmolality myoinositol, and redox potential
PKC activation
Altered cell function
• Renal, vascular, connective tissue effects
• Cytokines, growth factors
Altered cell function
Altered enzyme function (cPLA2, Na,K-ATPase)
Altered gene expression
Growth factors
Complications of diabetes

FIGURE 333-7 Possible molecular mechanisms of diabetes-related complications. AGEs, advanced glycation end products; PKC, protein kinase C; DAG, diacylglycerol; cPLA$_2$, phospholipase A$_2$; Na,K-ATPase, sodium-potassium ATPase.

inopathy and decreases after laser photocoagulation. Transforming growth factor β (TGF-β) is increased in diabetic nephropathy and appears to stimulate 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.

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 certain processes predominate in certain organs. Finally, oxidative stress and free radical generation, as a consequence of the hyperglycemia, may also promote the development of complications.

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 then evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with intense 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 HbA1c (7.2%) than individuals in the conventional diabetes management group (HbA1c of 9.0%).

Results from 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 sight, 5.8 additional years free from end-stage renal disease (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 as 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 HbA1c values (Fig. 333-8), suggesting that at any HbA1c level, an improvement in glycemic control is beneficial. Therefore, there is no threshold beneath which the HbA1c 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 HbA1c level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

Considerable debate has emerged as to whether the DCCT findings are applicable to individuals with type 2 DM, in whom insulin resistance, hyperinsulinemia, and obesity predominate. Concerns have been raised that therapies associated with weight gain and additional insulin therapy may worsen underlying insulin resistance and hyperinsulinemia. Despite these concerns, most available data support extrapolation of the results of the DCCT to individuals with type 2 DM.

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This complex and important 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 HbA1c of 7.0%, compared to a 7.9% HbA1c in the standard treatment group. The UKPDS demonstrated that each percentage point reduction in HbA1c was associated with a 35% reduction in microvascular complications, a 25% reduction in DM-related deaths, and a 7% reduction in all-cause mortality. As in the DCCT, there was a continuous relationship between glycemic control and development of complications. Although there was no statistically significant effect of

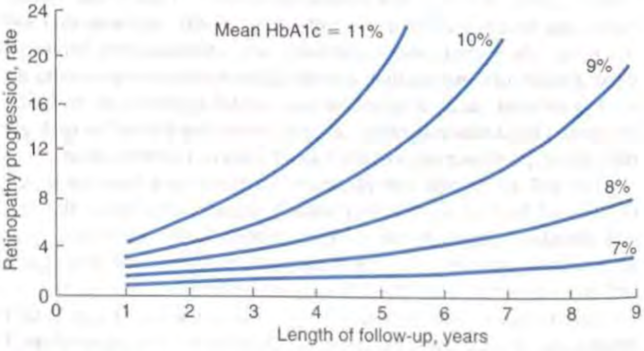

FIGURE 333-8 Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different HbA1c values. *(Adapted from The Diabetes Control and Complications Trial Research Group, Diabetes 44: 968, 1995)*

glycemic control on cardiovascular complications, there was a 16% reduction in fatal and nonfatal myocardial infarctions.

One of the major findings of the UKPDS was the observation 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%). 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 high-density lipoprotein (HDL).

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 with a presumably 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 **(see Plate IV-15)**. 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.

The appearance of neovascularization in response to retinal hypoxia is the hallmark of *proliferative diabetic retinopathy.* These newly formed vessels may appear at 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 a clear opportunity for early detection and treatment of diabetic retinopathy (discussed below). In contrast, *clinically significant macular edema* may appear when only nonproliferative retinopathy is present. Fluorescein angiography is often 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. 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 on the development of retinopathy than either the duration of DM or the degree of glycemic control.

℞ **TREATMENT** The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic control will greatly 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 should be considered 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.

Equally as important as glycemic control are regular, comprehensive eye examinations 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 properly. The treatment of diabetic eye disease requires an ophthalmologist experienced in 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 also.

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia (Fig. 334-7). The mechanisms by which chronic hyperglycemia leads to ESRD, though incompletely defined, involve the following: interaction of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration, 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 receptors. Smoking accelerates the decline in renal function.

The natural history of diabetic nephropathy is shown schematically in Fig. 333-9 and is characterized by a fairly predictable pattern of events. Although this sequence of events was defined for individuals with type 1 DM, a similar pattern is also likely in type 2 DM. Glomerular hyperfusion and renal hypertrophy occur in the first years after the onset of DM and are reflected by an increased 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). *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. The appearance of microalbuminuria (incipient nephropathy) in type 1 DM is a very important predictor of progression to overt proteinuria (>300 mg/d). 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 nephropathy becomes overt, the pathologic changes are likely irreversible.

The nephropathy that develops in type 2 DM differs from that of

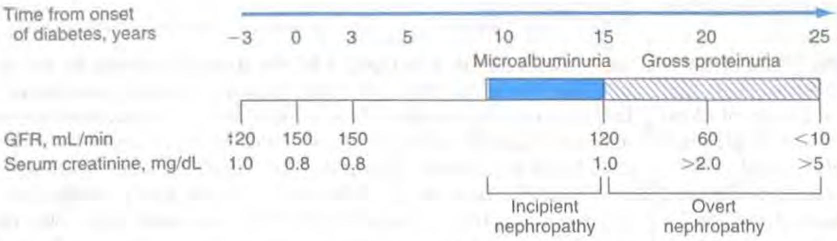

FIGURE 333-9 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. *(Adapted from DeFronzo RA, in Therapy for Diabetes Mellitus and Related Disorders, 1998)*

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 type 2 DM; and (3) microalbuminuria may be less predictive of progression to overt nephropathy in type 2 DM. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure, prostate disease, or infection.

Other renal problems may also occur in individuals with DM. Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) occurs in many individuals with DM. These individuals develop a propensity to hyperkalemia, which may be exacerbated by medications [especially angiotensin-converting enzyme (ACE) inhibitors]. Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Individuals with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored for several days following the procedure.

℞ **TREATMENT** The optimal therapy for diabetic nephropathy is prevention. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. The recommended strategy for detecting microalbuminuria is outlined in Fig. 333-10. Interventions effective in slowing progression from microalbuminuria to overt nephropathy include: (1) near normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors.

Improved glycemic control reduces the rate at which microalbuminuria appears and progresses in both type 1 and type 2 DM. However, once overt nephropathy exists, it is unclear whether improved glycemic control will slow progression of renal disease. During the phase of declining renal function, insulin requirements may fall as the kidney is a site of insulin degradation. Furthermore, glucose-lowering medications (sulfonylureas and metformin) may accumulate and are contraindicated in renal insufficiency.

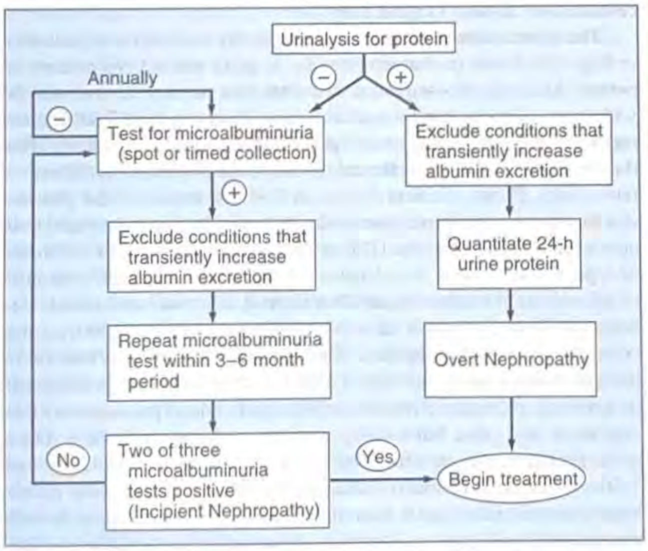
Urinalysis for protein
Annually
⊖
⊕
⊖
Test for microalbuminuria (spot or timed collection)
Exclude conditions that transiently increase albumin excretion
⊕
Exclude conditions that transiently increase albumin excretion
Quantitate 24-h urine protein
Repeat microalbuminuria test within 3–6 month period
Overt Nephropathy
No
Two of three microalbuminuria tests positive (Incipient Nephropathy)
Yes
Begin treatment

FIGURE 333-10 Screening for microalbuminuria. *(Adapted from DeFronzo RA, in Therapy for Diabetes Mellitus and Related Disorders, 1998)*

Many individuals with type 1 or type 2 DM develop hypertension. Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at <130/85 mmHg in diabetic individuals without proteinuria. A slightly lower blood pressure (120/80) should be targeted for individuals with microalbuminuria or overt nephropathy. Treatment of hypertension is discussed below.

ACE inhibitors reduce the progression of overt nephropathy in individuals with type 1 or type 2 DM and should be prescribed in individuals with type 1 or type 2 DM and microalbuminuria. After 2 to 3 months of therapy, measurement of proteinuria should be repeated and the drug dose increased until either the albuminuria disappears or the maximum dose is reached. If an ACE inhibitor has an unacceptable side-effect profile (hyperkalemia, cough, and renal insufficiency), angiotensin II receptor blockers and calcium channel blockers (phenylalkylamine class) are alternatives. However, their efficacy in slowing the fall in glomerular filtration rate is not proven. Blood pressure control with any agent is extremely important, but a drug-specific benefit in diabetic nephropathy, independent of blood pressure control, has been shown only for ACE inhibitors.

A consensus panel of the American Diabetes Association (ADA) suggests modest restriction of protein intake in diabetic individuals with microalbuminuria (0.8 g/kg per day, which is the adult Recommended Daily Allowance, and about 10% of the daily caloric intake). Protein intake should be restricted further in individuals with overt diabetic nephropathy (0.6 g/kg per day), though conclusive proof of the efficacy of protein restriction is lacking.

Nephrology consultation should be considered after the diagnosis of early nephropathy. Once overt nephropathy ensues, the likelihood of ESRD is very high. As compared to nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (autonomic neuropathy, loss of reflex tachycardia), more difficult vascular access, and accelerated progression of retinopathy. Survival after the onset of ESRD is shorter in the diabetic population compared to nondiabetics with similar clinical features. Atherosclerosis is the leading cause of death in diabetic individuals on dialysis, and hyperlipidemia should be aggressively treated. Renal transplantation from a living-related donor is the preferred therapy but requires chronic immunosuppression. Combined pancreas-kidney transplant offers the promise of normoglycemia but requires substantial expertise.

NEUROPATHY AND DIABETES MELLITUS Diabetic neuropathy occurs in approximately 50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of *diabetic* neuropathy should be made only after other possible etiologies are excluded (Chap. 378).

Polyneuropathy/Mononeuropathy The most common form of diabetic neuropathy is distal symmetric *polyneuropathy*. It most frequently presents with distal sensory loss. Hyperesthesia, parathesia, and pain also occur. Any combination of these symptoms may develop as neuropathy progresses. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense. Parethesia is characteristically perceived as a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, and a sensory deficit in the lower extremities persists.

Diabetic polyradiculopathy is a syndrome characterized by severe disabling pain in the distribution of one or more nerve roots. It may be accompanied by motor weakness. Intercostal or truncal radiculopathy causes pain over the thorax or abdomen. Involvement of the lumbar plexus or femoral nerve may cause pain in the thigh or hip and may be associated with muscle weakness in the hip flexors or extensors (diabetic amyotrophy). Fortunately, diabetic polyradiculopathies are usually self-limited and resolve over 6 to 12 months.

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. A vascular etiology is favored, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and opthalmoplegia with normal papillary constriction to light. Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

Autonomic Neuropathy Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including: the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy. Gastroparesis and bladder-emptying abnormalities are also likely related to the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of skin ulceration. Autonomic neuropathy may reduce counterregulatory hormone release, leading to an inability to sense hypoglycemia appropriately (*hypoglycemia unawareness*; Chap. 334), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

℞ **TREATMENT** Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be pursued and will improve nerve conduction velocity, but the symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Avoidance of neurotoxins (alcohol), supplementation with vitamins for possible deficiencies (B_{12}, B_6, folate; Chap. 75), and symptomatic treatment are the mainstays of therapy. Aldose reductase inhibitors do not currently offer significant symptomatic relief. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae; consequently, prevention of such problems is of paramount importance. Since the pain of acute diabetic neuropathy may resolve over the first year, analgesics may be discontinued as progressive neuronal damage from DM occurs. Chronic, painful diabetic neuropathy is difficult to treat but may respond to tricyclic antidepressants (amitriptyline, desipramine, nortriptyline), gabapentin, nonsteroidal anti-inflammatory agents (avoid in renal dysfunction), and other agents (mexilitine, phenytoin, carbamazepine, capsaicin cream). Referral to a pain management center may be necessary.

Therapy of orthostatic hypotension secondary to autonomic neuropathy is difficult. A variety of agents have limited success (fludrocortisone, midodrine, clonidine, octreotide, and yohimbine) but have significant side effects. Nonpharmacologic maneuvers (adequate salt intake, avoidance of dehydration and diuretics, and lower extremity support hose) may offer some benefit.

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION Long-standing type 1 and 2 DM may affect the motility and function of gastrointestinal (GI) and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). *Gastroparesis* may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal is the best study to document delayed gastric emptying, but noninvasive "breath tests" following ingestion of a radiolabeled meal are under development. Though parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, is a common feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac sprue because of its increased frequency. Esophageal dysfunction in long-standing DM is common but usually asymptomatic.

Diabetic autonomic neuropathy may lead to genitourinary dysfunction including cystopathy, erectile dysfunction, and female sexual dysfunction (reduced sexual desire, dyspareunia, reduced vaginal lubrication). Symptoms of diabetic cystopathy begin with an inability to sense a full bladder and a failure to void completely (Chap. 48). As bladder contractility worsens, bladder capacity and the postvoid residual increase, leading to symptoms of urinary hesitancy, decreased voiding frequency, incontinence, and recurrent urinary tract infections. Diagnostic evaluation includes cystometry and urodynamic studies.

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy. Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

℞ **TREATMENT** Current treatments for these complications of DM are inadequate. Improved glycemic control should be a primary goal, as some aspects (neuropathy, gastric function) may improve as near-normoglycemia is achieved. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Cisapride (10 to 20 mg before each meal) is probably the most effective medication but has been removed from use in the U.S. market except under special circumstances. Other agents with some efficacy include dopamine agonists (metoclopramide, 5 to 10 mg, and domperidone, 10 to 20 mg, before each meal) and bethanechol (10 to 20 mg before each meal). Erythromycin interacts with the motilin receptor and may promote gastric emptying. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically with loperamide but may respond to clonidine at higher doses (0.6 mg tid) or octreotide (50 to 75 μg tid subcutaneously). Treatment of bacterial overgrowth with antibiotics is sometimes useful (Chap. 286).

Diabetic cystopathy should be treated with timed voiding or self-catherization. Medications (bethanechol) are inconsistently effective. The drug of choice for erectile dysfunction is sildenafil, but the efficacy in individuals with DM is slightly lower than in the nondiabetic population (Chap. 51). Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

CARDIOVASCULAR MORBIDITY AND MORTALITY Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in several cardiovascular diseases in DM including peripheral vascular disease, congestive heart failure, coronary artery disease, myocardial infarction, and sudden death (risk increase from one- to fivefold). The American Heart Association recently designated DM as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). Because of the extremely high frequency of underlying cardiovascular disease in individuals with diabetes (especially in type 2 DM), evidence of atherosclerotic vascular disease should be sought in the individual with diabetes who has symptoms suggestive of cardiac ischemia, peripheral or carotid arterial disease, a resting electrocardiogram indicative of prior infarction, plans to initiate an exercise program, proteinuria, or two other cardiac risk factors (ADA recommendations). The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures.

The increase in morbidity and mortality appears to relate to the synergism of hyperglycemia with other cardiovascular risk factors. For example, after controlling for all known cardiovascular risk factors, type 2 DM increases the cardiovascular death rate by twofold in men and fourfold in women. Risk factors for macrovascular disease in diabetic individuals include dyslipidemia, hypertension, obesity, reduced physical activity, and cigarette smoking. Additional risk factors specific to the diabetic population include microalbuminuria, gross proteinuria, an elevation in serum creatinine, and altered platelet function. Insulin resistance, as reflected by elevated serum insulin levels, is associated with an increased risk of cardiovascular complications in individuals with and without DM. Individuals with insulin resistance and type 2 DM have elevated levels of plasminogen activator inhibitors (especially PAI-1) and fibrinogen, which enhances the coagulation process and impairs fibrinolysis, thus favoring the development of thrombosis.

Despite proof that improved glycemic control reduces microvascular complications in DM, it is possible that macrovascular complications may be unaffected or even worsened by such therapy. Concerns about the anabolic and atherogenic potential of insulin remain, since in nondiabetic individuals, higher serum insulin levels (indicative of insulin resistance) are associated with a greater risk of cardiovascular morbidity and mortality. In the DCCT, the number of cardiovascular events did not differ between the standard and intensively treated groups. However, the duration of DM in these individuals was relatively short, and the total number of events was very low. An improvement in the lipid profile of individuals in the intensive group [lower total and low-density lipoprotein (LDL) cholesterol, lower triglycerides] suggested that intensive therapy may reduce the risk of cardiovascular morbidity and mortality associated with DM. In the UKPDS, improved glycemic control did not conclusively reduce cardiovascular mortality. Importantly, treatment with insulin and the sulfonylureas did not appear to increase the risk of cardiovascular disease in individuals with type 2 DM, refuting prior claims about the atherogenic potential of these agents.

In addition to coronary artery disease, cerebrovascular disease is increased in individuals with DM (threefold increase in stroke). Individuals with DM have an increased incidence of congestive heart failure (diabetic cardiomyopathy). The etiology of this abnormality is probably multifactorial and includes factors such as myocardial ischemia from atherosclerosis, hypertension, and myocardial cell dysfunction secondary to chronic hyperglycemia.

℞ **TREATMENT** In general, the treatment of coronary disease is no different in the diabetic individual (Chap. 244), though overall prognosis after myocardial infarction is worse in the diabetic population. Revascularization procedures for coronary artery disease, including percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG), are less efficacious in the diabetic individual. Initial success rates of PTCA in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates. Perioperative mortality from CABG is not altered in DM, but both short- and long-term survival are reduced. Recent trials indicate that diabetic individuals with multivessel coronary artery disease or who recently suffered a Q-wave myocardial infarction have better long-term survival with CABG than PTCA.

Results of studies investigating the effect of intensive diabetes management on survival rates and cardiovascular events after myocardial infarction have been conflicting. In the face of conflicting data, the ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in all individuals with DM. Despite past trepidation about using beta blockers in individuals who have diabetes, these agents clearly benefit diabetic patients after myocardial infarction, analogous to the benefit in nondiabetic individuals. ACE inhibitors may also be particularly beneficial in reducing mortality after myocardial infarction in patients with DM.

Antiplatelet therapy reduces cardiovascular events in individuals with DM who have coronary artery disease. Current recommendations by the ADA suggest the use of aspirin as secondary prevention of additional coronary events. Although data demonstrating efficacy in primary prevention of coronary events are lacking, antiplatelet therapy should be considered, especially in diabetic individuals with other coronary risk factors such as hypertension, smoking, or hyperlipidemia. The aspirin dose (81 to 325 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not have detrimental effects on renal function or hypertension, nor does it influence the course of diabetic retinopathy or maculopathy.

Cardiovascular Risk Factors • ***Dyslipidemia*** Individuals with DM may have several forms of dyslipidemia (Chap. 344). Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be aggressively detected and treated as part of comprehensive diabetes care (Fig. 333-11). The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

According to guidelines of the ADA and the American Heart Association, the lipid profile in diabetic individuals without cardiovascular disease (primary prevention) should be: LDL < 3.4 mmol/L (130 mg/dL); HDL > 0.9 mmol/L (35 mg/dL) in men and >1.2 mmol/L

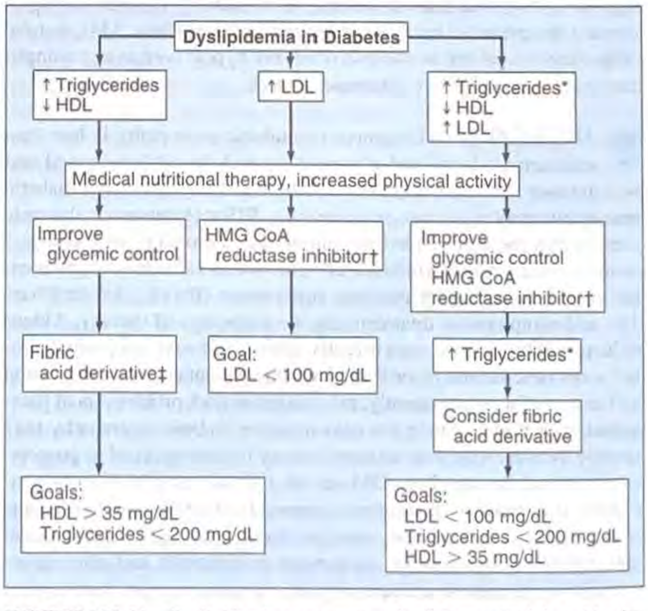
Dyslipidemia in Diabetes
↑ Triglycerides
↓ HDL
↑ LDL
↑ Triglycerides*
↓ HDL
↑ LDL
Medical nutritional therapy, increased physical activity
Improve glycemic control
HMG CoA reductase inhibitor†
Improve glycemic control HMG CoA reductase inhibitor†
Fibric acid derivative‡
Goal: LDL < 100 mg/dL
↑ Triglycerides*
Consider fibric acid derivative
Goals: HDL > 35 mg/dL Triglycerides < 200 mg/dL
Goals: LDL < 100 mg/dL Triglycerides < 200 mg/dL HDL > 35 mg/dL

FIGURE 333-11 Dyslipidemia management in diabetes. *Triglycerides increased but <400 mg/dL. †Second line treatment: fibric acid derivative or bile acid–binding resin. ‡Alternative treatment: high dose HMG CoA reductase inhibitor. The level of HDL in women should be 10 mg/dl higher.

(45 mg/dL) in women; and triglycerides < 2.3 mmol/L (200 mg/dL). In diabetic individuals with cardiovascular disease, the LDL goal is < 2.6 mmol/L (100 mg/dL). Because of the risk of cardiovascular disease in diabetic individuals, many authorities recommend that optimal lipid levels for all individuals with DM (with or without cardiovascular disease) should be: LDL < 2.6 mmol/L (100 mg/dL), HDL > 1.15 mmol/L (45 mg/dL) in men and > 1.41 mmol/L (55 mg/dL) in women; and triglycerides < 2.3 mmol/L (200 mg/dL). The ADA recommends dietary modification in diabetic individuals without cardiovascular disease and a LDL cholesterol of 2.6 to 3.3 mmol/L (100 to 129 mg/dL). If multiple cardiovascular risk factors are present, the goal should be a LDL < 2.6 mmol/L (100 mg/dL) even without known cardiovascular disease.

Almost all studies of diabetic dyslipidemia have been performed in individuals with type 2 DM because of the greater frequency of dyslipidemia in this form of diabetes. Interventional studies have shown that the beneficial effects of LDL reduction are similar in the diabetic and nondiabetic populations. Large prospective trials of primary and secondary intervention for coronary heart disease have included a small number of individuals with type 2 DM, and subset analyses have consistently found that reductions in LDL reduce cardiovascular events and morbidity in individuals with DM. Most clinical trials used HMG CoA reductase inhibitors, although a fibric acid derivative was also beneficial in one trial. No prospective studies have addressed similar questions in individuals with type 1 DM.

Based on the guidelines provided by the ADA and the American Heart Association, the order of priorities in the treatment of hyperlipidemia is: (1) lower the LDL cholesterol, (2) raise the HDL cholesterol, and (3) decrease the triglycerides. A treatment strategy depends on the pattern of lipoprotein abnormalities (Fig. 333-11). Initial therapy for all forms of dyslipidemia should include dietary changes, as well as the same life-style modifications recommended in the nondiabetic population (smoking cessation, control of blood pressure, weight loss, increased physical activity). The dietary recommendations for individuals with DM are similar to those advocated by the National Cholesterol Education Program (Chap. 344) and include an increase in monounsaturated fat and carbohydrates and a reduction in saturated fats and cholesterol. Though viewed as important, the response to dietary alterations is often modest [<0.6-mmol/L (<25-mg/dL) reduction in the LDL]. Improvement in glycemic control will lower triglycerides and have a modest beneficial effect on raising HDL. Most medications that improve glycemic control are useful in lowering triglycerides and may raise the HDL slightly. Though fibric acid derivatives have some efficacy and are well tolerated, nicotinic acid may worsen glycemic control and increase insulin resistance; thus, niacin is relatively contraindicated in diabetic patients on oral glucose-lowering agents. As noted above, HMG CoA reductase inhibitors have proven benefit in patients with DM, even with modest elevations in LDL. Combination therapy with an HMG CoA reductase inhibitor and fibric acid derivative may be useful but increases the possibility of myositis. Bile acid–binding resins should not be used if hypertriglyceridemia is present.

Hypertension Hypertension can accelerate other complications of DM, particularly cardiovascular disease and nephropathy. Hypertension therapy should first emphasize life-style modifications such as weight loss, exercise, stress management, and sodium restriction (Chap. 35). Antihypertensive agents should be selected based on the advantages and disadvantages of the therapeutic agent in the context of an individual patient's risk factor profile. ACE inhibitors are glucose- and lipid-neutral and thus positively impact the cardiovascular risk profile. For example, captopril actually improves insulin resistance, reduces LDL slightly, and increases HDL slightly. In one study of nondiabetic individuals, the ACE inhibitor ramipril reduced the risk of developing type 2 DM. Other effective agents include α-adrenergic blockers (prazocin, terazosin, doxazosin), calcium channel blockers, beta blockers (both β_1 selective and nonselective), thiazide diuretics (hydrochlorothiazide and its derivatives), central adrenergic antagonists (clonidine, methyldopa), and vasodilators (minoxidil, hydralazine). DM-related considerations include the following:

1. α-Adrenergic blockers slightly improve insulin resistance and positively impact the lipid profile, whereas beta blockers and thiazide diuretics can increase insulin resistance, negatively impact the lipid profile, and slightly increase the risk of developing type 2 diabetes.
2. Beta blockers, often questioned because of the potential masking of hypoglycemic symptoms, are effective agents and hypoglycemic events are rare when cardioselective (β_1) agents are used.
3. Central adrenergic antagonists and vasodilators are lipid- and glucose-neutral.
4. Sympathetic inhibitors and α-adrenergic blockers may be associated with orthostatic hypotension in the diabetic individual with autonomic neuropathy.
5. Calcium channel blockers are glucose- and lipid-neutral, and some evidence suggests that they reduce cardiovascular morbidity and mortality in type 2 DM, particularly in elderly patients with systolic hypertension.

If microalbuminuria or overt albuminuria is present, the optimal antihypertensive agent is an ACE inhibitor. If albumin excretion is normal, then an ACE inhibitor or other antihypertensive agent may be used. Low-dose diuretics and beta blockers are sometimes preferred as initial agents because of their clear efficacy in the nondiabetic population. Since hypertension is often difficult to control with a single agent (especially in type 2 DM), multiple antihypertensive agents are usually required when blood pressure goals (<130/85 mmHg) are not achieved. In this setting, long-acting calcium channel antagonists should be considered as additional, or second-line, agents, as these drugs appear to provide protection against cardiovascular events. ACE inhibitors are contraindicated in pregnant diabetic patients and those anticipating pregnancy. Because of the high prevalence of atherosclerotic disease in individuals with DM, the possibility of renovascular hypertension should be considered when the blood pressure is not readily controlled.

LOWER EXTREMITY COMPLICATIONS DM is the leading cause of nontraumatic lower extremity amputation in the United States. Foot ulcers and infections are also a major source of morbidity in individuals with DM. The reasons for the increased incidence of these disorders in DM are complex and involve the interaction of several pathogenic factors: neuropathy, abnormal foot biomechanics, peripheral vascular disease, and poor wound healing. The peripheral sensory neuropathy interferes with normal protective mechanisms and allows the patient to sustain major or repeated minor trauma to the foot, often without knowledge of the injury. Disordered proprioception causes abnormal weight bearing while walking and subsequent formation of callus or ulceration. Motor and sensory neuropathy leads to abnormal foot muscle mechanics and to structural changes in the foot (hammer toe, claw toe deformity, prominent metatarsal heads). Autonomic neuropathy results in anhidrosis and altered superficial blood flow in the foot, which promote drying of the skin and fissure formation. Peripheral vascular disease and poor wound healing impede resolution of minor breaks in the skin, allowing them to enlarge and to become infected.

Approximately 15% of individuals with DM develop a foot ulcer, and a significant subset of those individuals will at some time undergo amputation (14 to 24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include: male sex, diabetes >10 years' duration, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), peripheral vascular disease, smoking, and history of previous ulcer or amputation. Glycemic control is also a risk factor—each 2% increase in the HbA1c increases the risk of a lower extremity ulcer by 1.6 times and the risk of lower extremity amputation by 1.5 times.

TREATMENT The optimal therapy for foot ulcers and amputations is prevention through identification of high-risk patients, education of the patient, and institution of measures to prevent ulceration. High-risk patients should be identified during the routine foot examination performed on all patients with DM (see "Ongoing Aspects of Comprehensive Diabetes Care," below). Patient education should emphasize: (1) careful selection of footwear, (2) daily inspection of the feet to detect early signs of poor-fitting footwear or minor trauma, (3) daily foot hygiene to keep the skin clean and moist, (4) avoidance of self-treatment of foot abnormalities and high-risk behavior (e.g., walking barefoot), and (5) prompt consultation with a health care provider if an abnormality arises. Patients at high risk for ulceration or amputation may benefit from evaluation by a foot care specialist. Interventions directed at risk factor modification include orthotic shoes and devices, callus management, nail care, and prophylactic measures to reduce increased skin pressure from abnormal bony architecture. Attention to other risk factors for vascular disease (smoking, dyslipidemia, hypertension) and improved glycemic control are also important.

Despite preventive measures, foot ulceration and infection are common and represent a potentially serious problem. Due to the multifactorial pathogenesis of lower extremity ulcers, management of these lesions must be multidisciplinary and often demands expertise in orthopedics, vascular surgery, endocrinology, podiatry, and infectious diseases. The plantar surface of the foot is the most common site of ulceration. Cellulitis without ulceration is also frequent and should be treated with antibiotics that provide broad-spectrum coverage, including anaerobes (see below).

An infected ulcer is a clinical diagnosis, since superficial culture of any ulceration will likely find multiple possible bacterial pathogens. The infection surrounding the foot ulcer is often the result of multiple organisms (gram-positive and -negative cocci and anaerobes), and gas gangrene may develop in the absence of clostridial infection. Cultures taken from the debrided ulcer base or from purulent drainage are most helpful. Wound depth should be determined by inspection and probing with a blunt-tipped sterile instrument. Plain radiographs of the foot should be performed to assess the possibility of osteomyelitis in chronic ulcers that have not responded to therapy. Nuclear medicine bone scans may be helpful, but overlying subcutaneous infection is often difficult to distinguish from osteomyelitis. Indium-labeled white cell studies are more useful in determining if the infection involves bony structures or only soft tissue, but they are technically demanding. Magnetic resonance imaging of the foot may be the most specific modality, although distinguishing bony destruction due to osteomyelitis from destruction secondary to Charcot arthropathy is difficult. If surgical debridement is necessary, bone biopsy and culture usually provide the answer.

Osteomyelitis is best treated by a combination of prolonged antibiotics and debridement of infected bone. The possible contribution of vascular insufficiency should be considered in all patients. Noninvasive blood-flow studies are often unreliable in DM, and angiography may be required, recognizing the risk of contrast-induced nephrotoxicity. Peripheral vascular bypass procedures are often effective in promoting wound resolution and in decreasing the need for amputation of the ischemic limb.

A growing number of possible treatments for diabetic foot ulcers exist, but they have yet to demonstrate clear efficacy in prospective, controlled trials. A recent consensus statement from the ADA identified six interventions with demonstrated efficacy in diabetic foot wounds: (1) off-loading, (2) debridement, (3) wound dressings, (4) appropriate use of antibiotics, (5) revascularization, and (6) limited amputation. Off-loading is the complete avoidance of weight bearing on the ulcer, which removes the mechanical trauma that retards wound healing. Bed rest and a variety of orthotic devices limit weight bearing on wounds or pressure points. Surgical debridement of neuropathic wounds is important and effective, but clear efficacy of other modalities for wound cleaning (enzymes, soaking, whirlpools) is lacking. Dressings promote wound healing by creating a moist environment and protecting the wound. Antiseptic agents and topical antibiotics should be avoided. Referral for physical therapy, orthotic evaluation, and rehabilitation may be useful once the infection is controlled.

Mild or non-limb-threatening infections can be treated with oral antibiotics (cephalosporin, clindamycin, amoxicillin/clavulanate, and fluoroquinolones), surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection. More severe ulcers may require intravenous antibiotics as well as bed rest and local wound care. Urgent surgical debridement may be required. Intravenous antibiotics should provide broad-spectrum coverage directed toward *Staphylococcus aureus*, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial regimens include cefotetan, ampicillin/sulbactam, or the combination of clindamycin and a fluoroquinolone. Severe infections, or infections that do not improve after 48 h of antibiotic therapy, require expansion of antimicrobial therapy to treat methicillin-resistant *S. aureus* (e.g., vancomycin) and *Pseudomonas aeruginosa*. If the infection surrounding the ulcer is not improving with intravenous antibiotics, reassessment of antibiotic coverage and reconsideration of the need for surgical debridement or revascularization are indicated. With clinical improvement, oral antibiotics and local wound care can be continued on an outpatient basis with close follow-up. As infection improves, a comprehensive assessment of modifiable risk factors for foot ulceration should be performed and should involve health professionals with expertise in podiatry, orthotics, vascular surgery, and orthopedics.

New information about wound biology has led to a number of new technologies (e.g., living skin equivalents and growth factors such as basic fibroblast growth factor) that may prove useful. Recombinant platelet-derived growth factor has some benefit and complements the basic therapies of off-loading, debridement, and antibiotics. Hyperbaric oxygen has been used, but rigorous proof of efficacy is lacking.

INFECTIONS Individuals with DM exhibit a greater frequency and severity of infection. The reasons for this increase include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization secondary to long-standing diabetes. Hyperglycemia likely aids the colonization and growth of a variety of organisms (*Candida* and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population. Examples of this latter category includes rhinocerebral mucormycosis and malignant otitis externa, which is usually secondary to *P. aeruginosa* infection in the soft tissue surrounding the external auditory canal. Malignant otitis externa begins with pain and discharge and may progress rapidly to osteomyelitis and meningitis. These infections should be sought, in particular, in patients presenting with NKHS.

Pneumonia, urinary tract infections, and skin and soft tissue infections are all more common in the diabetic population. In general, the organisms that cause pulmonary infections are similar to those found in the nondiabetic population; however, gram-negative organisms, *S. aureus*, and *Mycobacterium tuberculosis* are more frequent pathogens. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as *Escherichia coli*, though several yeast species (*Candida* and *Torulopsis glabrata*) are commonly observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic cystopathy. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis is increased. Poor glycemic control is a common denominator in individuals with these infections. Diabetic individuals have an increased rate of colonization of *S. aureus* in the skin folds and nares. Diabetic patients also have a greater risk of postoperative wound infections.

DERMATOLOGIC MANIFESTATIONS The most common skin manifestations of DM are protracted wound healing and skin ulcerations. Diabetic dermopathy, sometimes termed *pigmented pretibial papules*, or "diabetic skin spots," begins as an erythematous area and evolves into an area of circular hyperpigmentation. These lesions result from minor mechanical trauma in the pretibial region and are more common in elderly men with DM. Bullous diseases (shallow ulcerations or erosions in the pretibial region) are also seen. *Necrobiosis lipoidica diabeticorum* is a rare disorder of DM that predominantly affects young women with type 1 DM, neuropathy, and retinopathy. It usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration. They may be painful. *Acanthosis nigricans* (hyperpigmented velvety plaques seen on the neck or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or localized *granuloma annulare* (erythematous plaques on the extremities or trunk) and *scleredema* (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population. *Lipoatrophy* and *lipohypertrophy* can occur at insulin injection sites but are unusual with the use of human insulin. Xerosis and pruritus are common and are relieved by skin moisturizers.

Approach to the Patient

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 complications begin to appear during the second decade of hyperglycemia. 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, prior medical conditions, 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, reduced glucose entry into muscle) 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 HbA1c levels, self-monitoring blood glucose results, frequency of hypoglycemia, presence of DM-specific complications, and assessment of the patient's knowledge about diabetes. The chronic 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 (see above). In addition, the presence of DM-related comorbidities should be sought (cardiovascular disease, hypertension, dyslipidemia).

Physical Examination In addition to a complete physical examination, special attention should be given to DM-relevant aspects such as weight or body mass index, retinal examination, orthostatic blood pressure, foot examination, peripheral pulses, and insulin injection sites. Careful examination of the lower extremities should seek evidence of peripheral neuropathy, calluses, superficial fungal infections, nail disease, and foot deformities (such as hammer or claw toes and Charcot foot) in order to identify sites of potential skin ulceration. Vibratory sensation (128-MHz tuning fork at the base of the great toe) and the ability to sense touch with a monofilament (5.07, 10-g monofilament) are useful to detect moderately advanced diabetic neuropathy. Since dental disease is more frequent in DM, the teeth and gums should also be examined.

Classification of DM in an Individual Patient The etiology of diabetes in an individual with new-onset disease can usually be assigned on the basis of clinical criteria. Individuals with type 1 DM tend to have the following characteristics: (1) onset of disease prior to age 30; (2) lean body habitus; (3) requirement of insulin as the initial therapy; (4) propensity to develop ketoacidosis; and (5) an increased risk of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, and vitiligo. In contrast, individuals with type 2 DM often exhibit the following features: (1) develop diabetes after the age of 30; (2) are usually obese (80% are obese, but elderly individuals may be lean); (3) may not require insulin therapy initially; and (4) may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or polycystic ovary syndrome. In type 2 DM, insulin resistance is often associated with abdominal obesity (as opposed to hip and thigh obesity) and hypertriglyceridemia. Although most individuals diagnosed with type 2 DM are older, the age of diagnosis appears to be declining in some ethnic groups, and there is a marked increase among overweight teenagers. On the other hand, some individuals (<10%) with the phenotypic appearance of type 2 DM do not have absolute insulin deficiency but have autoimmune markers suggestive of type 1 DM. Thus, despite the revised classification of DM, it is remains difficult to categorize some patients unequivocally. Individuals who deviate from the clinical profile of type 1 and type 2 DM, or who have other associated defects such as deafness, pancreatic exocrine disease, and other endocrine disorders, should be classified accordingly (Table 333-1).

Laboratory Assessment The laboratory assessment should first determine whether the patient meets the diagnostic criteria for DM (Table 333-2) and should then assess the degree of glycemic control (HbA1c, discussed below). In addition to the standard laboratory evaluation, the patient should be screened for DM-associated conditions (e.g., microalbuminuria, dyslipidemia, thyroid dysfunction). Individuals at high risk for cardiovascular disease should be screened for asymptomatic coronary artery disease by appropriate cardiac stress testing, when indicated.

The classification of the type of DM does not usually require laboratory assessments. Serum insulin or C-peptide measurements do not clearly distinguish type 1 from type 2 DM at the time of diabetes onset; a low C-peptide level merely confirms a patient's need for insulin. Conversely, many individuals with new-onset type 1 DM retain some C-peptide production. Measurement of islet cell antibodies at the time of diabetes onset may be useful if the type of DM is not clear based on the characteristics discussed above, but this knowledge does not usually alter therapy, which is based primarily on empirical metabolic features.

LONG-TERM TREATMENT

OVERALL PRINCIPLES The goals of therapy for type 1 or type 2 DM are to: (1) eliminate symptoms related to hyperglycemia, (2) reduce or eliminate the long-term microvascular and macrovascular complications of DM, and (3) allow the patient to achieve as normal a life-style as possible. To reach these goals, the physician should identify a target level of glycemic control for each patient, provide the patient with the educational and pharmacologic resources necessary to reach this level, and monitor/treat DM-related complications. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL), and thus most DM treatment focuses on achieving the second and third goals.

The care of an individual with either type 1 or type 2 DM requires a multidisciplinary team. Central to the success of this team are the patient's participation, input, and enthusiasm, all of which are essential for optimal diabetes management. Members of the health care team include the primary care provider and/or the endocrinologist or diabetologist, a certified diabetes educator, and a nutritionist. In addition, when the complications of DM arise, subspecialists (including neurologists, nephrologists, vascular surgeons, cardiologists, ophthalmologists, and podiatrists) with experience in DM-related complications are essential.

A number of names are sometimes applied to different approaches to diabetes care, such as intensive insulin therapy, intensive glycemic control, and "tight control." The current chapter, however, will use the term *comprehensive diabetes care* to emphasize the fact that optimal diabetes therapy involves more than plasma glucose management. Though glycemic control is central to optimal diabetes therapy, comprehensive diabetes care of both type 1 and type 2 DM should also detect and manage DM-specific complications and modify risk factors for DM-associated diseases.

In addition to assessing the physical aspects of the patient with DM, the physician and members of the diabetes management team should consider social, family, financial, cultural, and employment-related issues that may have an impact on diabetes care. With this information, the physician can work with the patient and his or her family to establish therapeutic goals and design a comprehensive and feasible plan for optimal diabetes care.

EDUCATION OF THE PATIENT ABOUT DM, NUTRITION, AND EXERCISE Patient participation is an essential component of comprehensive diabetes care. The patient with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose. Along with improved compliance, patient education allows individuals with DM to assume greater responsibility for their care. Patient education should be viewed as a continuing process with regular visits for reinforcement; it should *not* be a process that is completed after one or two visits to a nurse educator or nutritionist.

Diabetes Education The diabetes educator is a health care professional (nurse, dietician, or pharmacist) with specialized patient education skills who is certified in diabetes education (indicating demonstrated skills in diabetes knowledge and education and certification by the American Association of Diabetes Educators). The educator is a vital member of the comprehensive diabetes care program and educates the patient about a number of issues important for optimal diabetes care, including self-monitoring of blood glucose; urine ketone monitoring (type 1 DM); insulin administration; guidelines for diabetes management during illnesses; management of hypoglycemia; foot and skin care; diabetes management before, during, and after exercise; and risk factor–modifying activities.

Nutrition *Medical nutrition therapy* (MNT) is a term used by the ADA to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss). Historically, nutrition has imposed restrictive, complicated regimens on the patient. Current practices have greatly changed, though many patients and health care providers still view the diabetic diet as monolithic and static. For example, modern MNT now includes foods with sucrose and seeks to modify other risk factors such as hyperlipidemia and hypertension rather than focusing exclusively on weight loss in individuals with type 2 DM. Like other aspects of DM therapy, MNT must be adjusted to meet the goals of the individual patient. Furthermore, MNT education is an important component of comprehensive diabetes care and should be reinforced by regular patient education. In general, the components of optimal MNT are similar for individuals with type 1 or type 2 DM (Table 333-8).

The goal of MNT in the individual with type 1 DM is to coordinate and match the caloric intake, both temporally and quantitatively, with the appropriate amount of insulin. MNT in type 1 DM and self-monitoring of blood glucose must be integrated to define the optimal insulin regimen. MNT must be flexible enough to allow for exercise, and the insulin regimen must allow for deviations in caloric intake. An important component of MNT in type 1 DM is to minimize the weight gain often associated with intensive diabetes management.

Table 333-8 Nutritional Recommendations for All Persons with Diabetes

- Protein to provide ~10–20% of kcal/d (~10% for those with nephropathy)
- Saturated fat to provide <10% of kcal/d (<7% for those with elevated LDL)
- Polyunsaturated fat to provide ≤10% of kcal
- Remaining calories to be divided between carbohydrate and monounsaturated fat, based on medical needs and personal tolerance
- Use of caloric sweeteners, including sucrose, is acceptable. Sugars must be accounted for so that the insulin demand they create is matched to available insulin
- Fiber (20–35 g/d) and sodium (≤3000 mg/d) levels as recommended for the general healthy population
- Cholesterol intake ≤300 mg/d
- The same precautions regarding alcohol use in the general population also apply to individuals with diabetes. In addition, alcohol may increase risk for hypoglycemia and therefore should be taken with food.

NOTE: LDL, low-density lipoprotein.
SOURCE: Adapted from Farkas-Hirsch, 1998.

The goals of MNT in type 2 DM are slightly different and address the greatly increased prevalence of cardiovascular risk factors (hypertension, dyslipidemia, obesity) and disease in this population. The majority of these individuals are obese, and weight loss is still strongly encouraged and should remain an important goal. Medical treatment of obesity is a rapidly evolving area and is discussed in Chap. 77. Hypocaloric diets and modest weight loss often result in rapid and dramatic glucose lowering in individuals with new-onset type 2 DM. Nevertheless, numerous studies document that long-term weight loss is uncommon. Therefore, current MNT for type 2 DM should emphasize modest caloric reduction, increased physical activity, and reduction of hyperlipidemia and hypertension. Increased consumption of soluble, dietary fiber may improve glycemic control in individuals with type 2 DM.

Exercise Exercise is an integral component of comprehensive diabetes care that can have multiple positive benefits (cardiovascular benefits, reduced blood pressure, maintenance of muscle mass, reduction in body fat, weight loss, etc.). For individuals with type 1 or type 2 DM, exercise is also useful for lowering plasma glucose (during and following exercise) and increasing insulin sensitivity.

Despite its benefits, exercise presents several challenges for individuals with DM because they lack the normal glucoregulatory mechanisms. Skeletal muscle is a major site for metabolic fuel consumption in the resting state, and the increased muscle activity during vigorous, aerobic exercise greatly increases fuel requirements. Individuals with type 1 DM are prone to either hyperglycemia or hypoglycemia during exercise, depending on the preexercise plasma glucose, the circulating insulin level, and the level of exercise-induced catecholamines. If the insulin level is too low, the rise in catecholamines may increase the plasma glucose excessively, promote ketone body formation, and possibly lead to ketoacidosis. Conversely, if the circulating insulin level is excessive, this relative hyperinsulinemia may reduce hepatic glucose production (decreased glycogenolysis, decreased gluconeogenesis) and increase glucose entry into muscle, leading to hypoglycemia.

To avoid exercise-related hyper- or hypoglycemia, individuals with type 1 DM should: (1) monitor blood glucose before, during, and after exercise; (2) delay exercise if blood glucose is >14 mmol/L (250 mg/dL), <5.5 mmol/L (100 mg/dL), or if ketones are present; (3) eat a meal 1 to 3 h before exercise and take supplemental carbohydrate feedings at least every 30 min during vigorous or prolonged exercise; (4) decrease insulin doses (based on previous experience) before exercise and inject insulin into a nonexercising area; and (5) learn individual glucose responses to different types of exercise and increase food intake for up to 24 h after exercise, depending on intensity and duration of exercise. In individuals with type 2 DM, exercise-related hypoglycemia is less common but can occur in individuals taking either insulin or sulfonylureas.

Because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, formal exercise tolerance testing may be warranted in diabetic individuals with any of the following: age ≥35 years, long-standing type 1 DM (>20 to 25 years' duration), microvascular complications of DM (retinopathy, microalbuminuria, or nephropathy), peripheral vascular disease, other risk factors of coronary artery disease, or autonomic neuropathy. Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, since this may lead to vitreous hemorrhage or retinal detachment.

MONITORING THE LEVEL OF GLYCEMIC CONTROL Optimal monitoring of glycemic control involves plasma glucose measurements by the patient and an assessment of long-term control by the physician (measurement of HbA1c and review of the patient's self-measurements of plasma glucose). These measurements are complementary: the patient's measurements provide a picture of short-term glycemic control, whereas the HbA1c reflects average glycemic control over the previous 2 to 3 months. Integration of both measurements provides an accurate assessment of the glycemic control achieved.

Self-Monitoring of Blood Glucose Self-monitoring of blood glucose (SMBG) is the standard of care in diabetes management and allows the patient to monitor his or her blood glucose at any time. In SMBG, a small drop of blood and an easily detectable enzymatic reaction allow measurement of the capillary plasma glucose. By combining glucose measurements with diet history, medication changes, and exercise history, the physician and patient can improve the treatment program.

The frequency of SMBG measurements must be individualized and adapted to address the goals of diabetes care as defined by the patient and the health care provider. Individuals with type 1 DM should routinely measure their plasma glucose four to eight times per day to estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses. Most individuals with type 2 DM require less frequent monitoring, though the optimal frequency of SMBG has not been clearly defined. Individuals with type 2 DM who are on oral medications should utilize SMBG as a means of assessing the efficacy of their medication and diet. Since plasma glucose levels fluctuate less in these individuals, one to two SMBG measurements per day (or fewer) may be sufficient. Individuals with type 2 DM who are on insulin should utilize SMBG more frequently than those on oral agents.

Two devices for continuous blood glucose monitoring have been recently approved by the U.S. Food and Drug Administration (FDA). The Glucowatch uses iontophoresis to assess glucose in interstitial fluid, whereas the Minimed device uses an indwelling subcutaneous catheter to monitor interstitial fluid glucose. Both devices utilize immobilized glucose oxidase to generate electrons in response to changing glucose levels. Though clinical experience with these devices is limited, they perform well in clinical trials and appear to provide useful short-term information about the patterns of glucose changes as well as an enhanced ability to detect hypoglycemic episodes.

Although urine glucose testing does not provide an accurate assessment of glycemic control, urine ketones are a sensitive indicator of early diabetic ketoacidosis and should be measured in individuals with type 1 DM when the plasma glucose is consistently 16.7 mmol/L (300 mg/dL); during a concurrent illness; or with symptoms such as nausea, vomiting, or abdominal pain.

Assessment of Long-Term Glycemic Control Measurement of glycated hemoglobin is the standard method for assessing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2 to 3 months, since erythrocytes have an average life span of 120 days. There are numerous laboratory methods for measuring the various forms of glycated hemoglobin, and these have significant interassay variations. Because of its superior specificity and reliability, the HbA1c assay performed by the high-performance liquid chromatography (HPLC) method has become the standard reference method for most glycated hemoglobin measurements. Since glycated hemoglobin measurements are usually compared to prior measurements, it is essential for the assay results to be comparable. Depending on the assay methodology for HbA1c, hemoglobinopathies, hemolytic anemia, and uremia may interfere with the HbA1c result.

Glycated hemoglobin or HbA1c should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. As the primary predictor of long-term complications of DM, the HbA1c should mirror, to a certain extent, the short-term measurements of SMBG. These two measurements are complementary in that recent intercurrent illnesses may impact the SMBG measurements but not the HbA1c. Likewise, postprandial and nocturnal hyperglycemia may not be detected by the SMBG of fasting and preprandial capillary plasma glucose but will be reflected in the HbA1c. When measured by HPLC, the HbA1c approximates the following mean plasma glucose values: an HbA1c of 6% is 6.6 mmol/L (120 mg/dL), 7% is 8.3 mmol/L (150 mg/dL), 8% is 10.0 mmol/L (180 mg/dL), etc. [A 1% rise in the HbA1c translates into a 1.7-mmol/L (30 mg/dL) increase in the mean glucose.] The degree of glycation of other proteins, such as albumin, has been used as an alternative indicator of glycemic control when the HbA1c is inaccurate (hemolytic anemia, hemoglobinopathies). The fructosamine assay (using albumin) is an example of an alternative measurement of glycemic control and reflects the glycemic status over the 2 to 4 prior weeks. Current consensus statements do not favor the use of alternative assays of glycemic control, as there are no studies to indicate whether such assays accurately predict the complications of DM.

℞ **TREATMENT** **Establishment of a Target Level of Glycemic Control** Because the complications of DM are related to glycemic control, normoglycemia or near normoglycemia is the desired, but often elusive, goal for most patients. However, normalization of the plasma glucose for long periods of time is extremely difficult, as demonstrated by the DCCT. Regardless of the level of hyperglycemia, improvement in glycemic control will lower the risk of diabetes complications (Fig. 333-8).

The target for glycemic control (as reflected by the HbA1c) must be individualized, and the health care provider should establish the goals of therapy in consultation with the patient after considering a number of medical, social, and life-style issues. Some important factors to consider include the patient's age, ability to understand and implement a complex treatment regimen, presence and severity of complications of diabetes, ability to recognize hypoglycemic symptoms, presence of other medical conditions or treatments that might alter the response to therapy, life-style and occupation (e.g., possible consequences of experiencing hypoglycemia on the job), and level of support available from family and friends.

The ADA has established suggested glycemic goals based on the premise that glycemic control predicts development of DM-related complications. In general, the target HbA1c should be <7.0% (Table 333-9). Other consensus groups (such as the Veterans Administration) have suggested HbA1c goals that take into account the patient's life expectancy at the time of diagnosis and the presence of microvascular complications. Such recommendations strive to balance the financial and personal costs of glycemic therapy with anticipated benefits (reduced health care costs, reduced morbidity). One limitation to this approach is that the onset of hyperglycemia in type 2 DM is difficult to ascertain and likely predates the diagnosis. Furthermore, though the life expectancy can be predicted for a patient population, the physician must treat an individual patient; consequently, the target HbA1c must be individualized to accommodate these other considerations.

Type 1 Diabetes Mellitus • ***General aspects*** Comprehensive diabetes care should be instituted in all individuals with type 1 DM and should involve attention to nutrition, exercise, and risk factor management in addition to insulin administration. The ADA recommendations for fasting and bedtime glycemic goals and HbA1c targets are summarized in Table 333-9. The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Because in-

Table 333-9 Ideal Goals for Glycemic Control[a]

Index	Normal Range	Goal	Additional Action Suggested
Average preprandial glucose, mmol/L (mg/dL)	<5.5 (100)	4.4–6.7 (80–120)	<4.4 (80) *or* >7.8 (140)
Average bedtime glucose, mmol/L (mg/dL)	<6.1 (110)	5.5–7.8 (100–140)	<5.5 (100) *or* >8.8 (160)
HbA1c, %	<6	<7	>8

[a] These values are for whole blood measurements, and home glucose-monitoring devices may report either whole blood or plasma glucose values. Plasma glucose values are 10–15% higher than whole blood values. The upper limit of the HbA1c reference range is 6.0% (mean 5.0%, with a standard deviation of 0.5%). These goals must be individualized for each patient and must consider the patient's age and other medical conditions.

SOURCE: Adapted from American Diabetes Association, 2000.

dividuals with type 1 DM lack endogenous insulin production, administration of basal, exogenous insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis. Likewise, postprandial insulin replacement should be appropriate for the carbohydrate intake and promote normal glucose utilization and storage.

Intensive management Intensive diabetes management is defined by the ADA as ". . . a mode of treatment for the person with DM that has the goal of achieving euglycemia or near-normal glycemia using all available resources to accomplish this goal." These resources include thorough and continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches glucose intake and insulin dose. Insulin regimens usually include multiple-component insulin regimens, multiple daily injections (MDI), or insulin infusion devices (all discussed below).

The benefits of intensive diabetes management and improved glycemic control include a reduction in the microvascular complications of DM and a possible delay or reduction in the macrovascular complications of DM. From a psychological standpoint, the patient experiences greater control over his or her diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the capability to alter insulin dosing with exercise. In addition, intensive diabetes management in pregnancy reduces fetal malformation and morbidity. Intensive diabetes management is also strongly encouraged in newly diagnosed patients with type 1 DM because it may prolong the period of C-peptide production, which may result in better glycemic control and a reduced risk of serious hypoglycemia.

Although intensive management confers impressive benefits, it is also accompanied by significant personal and financial costs and is therefore not appropriate for all individuals. It requires a combination of dedication, persistence, and motivation on the part of the patient, as well as medical, educational, nursing, nutritional, and psychological expertise on the part of the diabetes management team. Circumstances in which intensive diabetes management should be strongly considered are listed in Table 333-10.

Insulin preparations Current insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin. Animal insulin (beef or pork) is no longer used. Human insulin has been formulated with distinctive pharmacokinetics to mimic physiologic insulin secretion (Table 333-11). In the United States, all insulin is formulated as U-100 (100 units/mL), whereas in some other countries it is available in other units (e.g., U-40 = 40 units/mL). One short-acting insulin formulation, lispro, is an insulin analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed by recombinant DNA technology. This insulin analogue has full biologic activity but less tendency toward subcutaneous aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. These characteristics are particularly advantageous for allowing entrainment of insulin injection and action to rising plasma glucose levels following meals, although improvement in HbA1c values have not been found consistently. The shorter duration of action also appears to be associated with a decreased number of hypoglycemic episodes, primarily because the decay of lispro action corresponds better to the decline in plasma glucose after a meal. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C-terminus of the B chain. Compared to NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is no pronounced peak. A lower incidence of hypoglycemia, especially at night, was reported in one trial with insulin glargine when compared to NPH insulin. Since glargine has only recently approved, clinical experience is limited. Additional insulin analogues are currently under development.

Basal insulin requirements are provided by intermediate (NPH or lente) or long-acting (ultralente or glargine) insulin formulations. These are usually combined with short-acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of intermediate and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially those of short-acting insulins). For example, the absorption of regular insulin is delayed when mixed for even short periods of time (<5 min) with lente or ultralente insulin, but not when mixed with NPH insulin. Lispro absorption is delayed by mixing with NPH but not ultralente. Insulin glargine should not be mixed with other insulins. The miscibility of human regular and NPH insulin allows for the production of combination insulins that contain 75% NPH and 25% regular (75/25), 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular. These combinations of insulin are more convenient for the patient but prevent adjustment of only one component of the insulin formulation. The alteration in insulin absorption when the patient mixes different insulin formulation should not discourage the patient from mixing insulin. However, the following guidelines should be followed: (1) mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing); (2) if possible, do not store insulin as a mixture; and (3) follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin.

Insulin regimens Representations of the various insulin regimens that may be utilized in type 1 DM are illustrated in Fig. 333-12. Although the insulin profiles are depicted as "smooth," symmetric curves, there is considerable patient-to-patient variation in the peak and duration. In all regimens, long-acting insulins (NPH, lente, ultralente, or glargine insulin) supply basal insulin, whereas prandial insulin is provided by either regular or lispro insulin. Lispro should be injected just before a meal; regular insulin is given 30 to 45 min prio to a meal.

A shortcoming of current insulin regimens is that injected insuli immediately enters the systemic circulation, whereas endogenous in

Table 333-10 Indications for Intensive Diabetes Management

- Otherwise healthy adults with either type 1 or type 2 diabetes (selected adolescents and older children)
- Purposeful, therapeutic attempt to avoid or lessen microvascular complications
- All pregnant women with diabetes; all women with diabetes who are planning pregnancy
- Management of labile diabetes
- Availability of health care professionals with appropriate expertise
- Patients who have had kidney transplantation for diabetic nephropathy

SOURCE: Adapted from Farkas-Hirsch, 1998.

sulin is secreted into the portal vein. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels. No insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance on short-acting insulin, and more frequent capillary plasma glucose measurements. In general, individuals with type 1 DM require 0.5 to 1.0 U/kg per day of insulin divided into multiple doses. Initial insulin-dosing regimens should be conservative; approximately 40 to 50% of the insulin should be given as basal insulin. A single daily injection of insulin is not appropriate therapy in type 1 DM.

Table 333-11 Pharmacokinetics of Insulin Preparations

Preparation	Time of Action			
	Onset, h	Peak, h	Effective Duration, h	Maximum Duration, h
Short-acting				
Lispro	<0.25	0.5–1.5	3–4	4–6
Regular	0.5–1.0	2–3	3–6	6–8
Intermediate-acting				
NPH	2–4	6–10	10–16	14–18
Lente	3–4	6–12	12–18	16–20
Long-acting				
Ultralente	6–10	10–16	18–20	20–24
Glargine	4	–[a]	24	>24
Combinations				
75/25–75% NPH, 25% regular	0.5–1	Dual	10–16	14–18
70/30–70% NPH, 30% regular	0.5–1	Dual	10–16	14–18
50/50–50% NPH, 50% regular	0.5–1	Dual	10–16	14–18

[a] Glargine has minimal peak activity.

SOURCE: Adapted from JS Skyler, in *Therapy for Diabetes Mellitus and Related Disorders*, 1998

One commonly used regimen consists of twice-daily injections of an intermediate insulin (NPH or lente) mixed with a short-acting insulin before the morning and evening meal (Fig. 333-12*A*). Such regimens usually prescribe two-thirds of the total daily insulin dose in the morning (with about two-thirds given as intermediate-acting insulin and one-third as short-acting) and one-third before the evening meal (with approximately one-half given as intermediate-acting insulin and one-half as short-acting). The drawback to such a regimen is that it enforces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals. Although it is simple and effective at avoiding severe hyperglycemia, it does not generate near-normal glycemic control in most individuals with type 1 DM. Moreover, if the patient's meal pattern or content varies or if physical activity is increased, hyperglycemia or hypoglycemia may result. Moving the intermediate insulin from before the evening meal to bedtime may avoid nocturnal hypoglycemia and provide more insulin as glucose levels rise in the early morning (so-called dawn phenomenon). The insulin dose in such regimens should be adjusted based on SMBG results with the following general assumptions: (1) the fasting glucose is primarily determined by the prior evening intermediate-acting insulin; (2) the pre-lunch glucose is a function of the morning short-acting insulin; (3) the pre-supper glucose is a function of the morning intermediate-acting insulin; and (4) the bedtime glucose is a function of the pre-supper, short-acting insulin.

Multiple-component insulin regimens refer to the combination of basal insulin; preprandial short-acting insulin; and changes in short-acting insulin doses to accommodate the results of frequent SMBG, anticipated food intake, and physical activity. Sometimes also referred to as *multiple daily injections*, such regimens offer the patient maximal flexibility in terms of life-style and the best chance for achieving near normoglycemia. One such regimen, shown in Fig. 333-12*B*, consists of a basal insulin with ultralente twice a day and preprandial lispro. The lispro dose is based on individualized algorithms that integrate the preprandial glucose and the anticipated carbohydrate intake. An alternative multiple-component insulin regimen consists of bedtime intermediate insulin, a small dose of intermediate insulin at breakfast (20 to 30% of bedtime dose), and preprandial short-acting insulin. There are numerous variations of these regimens that can be optimized for individual patients. Frequent SMBG (four to 8 times per day) is absolutely essential for these types of insulin regimens.

Continuous subcutaneous insulin infusion (CSII) is another multiple-component insulin regimen (Fig. 333-12*C*). Sophisticated insulin infusion devices are now available that can accurately deliver small doses of insulin (microliters per hour). For example, multiple basal infusion rates can be programmed to: (1) accommodate nocturnal versus daytime basal insulin requirement, (2) alter infusion rate during periods of exercise, or (3) select different waveforms of insulin infusion. A preprandial insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, which follow individualized algorithms that account for preprandial plasma glucose and anticipated carbohydrate intake. These devices require a health professional with considerable experience with insulin infusion devices and very frequent patient interactions with the diabetes management team. Insulin infusion devices present unique challenges, such as infection at the infusion site, unexplained hyperglycemia because the infusion set becomes obstructed, or diabetic ketoacidosis if the pump becomes disconnected. Since most physicians use lispro insulin in CSII, the extremely short half-life of this insulin quickly leads to

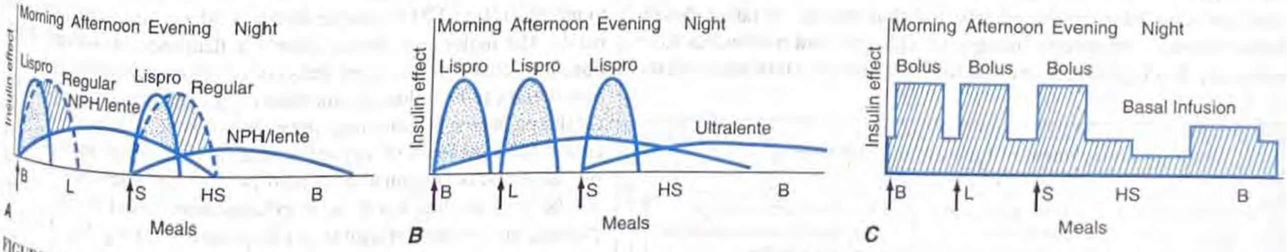

FIGURE 333-12 Representative insulin regimens for the treatment of diabetes. For each panel, the y-axis shows the amount of insulin effect and the x-axis shows the time of day. B, breakfast; L, lunch; S, supper; HS, bedtime; CSII, continuous subcutaneous insulin infusion. The time of insulin injection is shown with a vertical arrow. The type of insulin is noted above each insulin curve. *A*. The injection of two shots of intermediate-acting insulin (NPH or lente) and short-acting insulin (lispro or regular). Only one formulation of short-acting insulin is used. *B*: A multiple-component insulin regimen consisting of two shots of ultralente each day to provide basal insulin coverage and three shots of Lispro to provide glycemic coverage for each meal. The ultralente doses are usually 10 to 12 h apart. *C*: Insulin administration by insulin infusion device is shown with the basal insulin and a bolus injection at each meal. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. *(Adapted from Intensive Diabetes Management, 2d ed, R. Farkas-Hirsch (ed). Alexandria, VA, American Diabetes Association, 1998)*

insulin deficiency if the delivery system is interrupted. Essential to the safe use of infusion devices is thorough patient education about pump function and frequent SMBG.

Type 2 Diabetes Mellitus • ***General aspects*** The goals of therapy for type 2 DM are similar to those in type 1: improved glycemic control with near normalization of the HbA1c. While glycemic control tends to dominate the management of type 1 DM, the care of individuals with type 2 DM must also include attention to the treatment of conditions associated with type 2 DM (obesity, hypertension, dyslipidemia, cardiovascular disease) and detection/management of DM-related complications (Fig. 333-13). DM-specific complications may be present in up to 20 to 50% of individuals with newly diagnosed type 2 DM. Reduction in cardiovascular risk is of paramount importance as this is the leading cause of mortality in these individuals.

Diabetes management should begin with MNT (discussed above). An exercise regimen to increase insulin sensitivity and promote weight loss should also be instituted. After MNT and increased physical activity have been instituted, glycemic control should be reassessed; if the patient's glycemic target is not achieved after 3 to 4 weeks of MNT, pharmacologic therapy is indicated. Pharmacologic approaches to the management of type 2 DM include both oral glucose-lowering agents and insulin; most physicians and patients prefer oral glucose-lowering agents as the initial choice. Any therapy that improves glycemic control reduces "glucose toxicity" to the islet cells and improves endogenous insulin secretion.

Glucose-lowering agents Recent advances in the therapy of type 2 DM have generated considerable enthusiasm for oral glucose-lowering agents that target different pathophysiologic processes in type 2 DM. Based on their mechanisms of action, oral glucose-lowering agents are subdivided into agents that increase insulin secretion, reduce glucose production, or increase insulin sensitivity (Table 333-12). Oral glucose-lowering agents (with the exception of α-glucosidase inhibitors) are ineffective in type 1 DM and should not be used for glucose management of severely ill individuals with type 2 DM. Insulin is sometimes the initial glucose-lowering agent.

INSULIN SECRETAGOGUES Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell (Fig. 333-1). These drugs are most effective in individuals with type 2 DM of relatively recent onset (<5 years), who have endogenous insulin production and tend to be obese. At maximum doses, first-generation sulfonylureas are similar in potency to second-generation agents but have a longer half-life, a greater incidence of hypoglycemia, and more frequent drug interactions (Table 333-13). Thus, second-generation sulfonylureas are generally preferred. An advantage to a more rapid onset of action is better coverage of the postprandial glucose rise, but the shorter half-life of such agents requires more than once-a-day dosing. Sulfonylureas reduce both fasting and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on SMBG. In general, sulfonylureas increase insulin acutely and thus should be taken shortly before a meal; with chronic therapy, though, the insulin release is more sustained. Replaglinide is not a sulfonylurea but also interacts with the ATP-sensitive potassium channel. Because of its short half-life, it is usually given with or immediately before each meal to reduce meal-related glucose excursions.

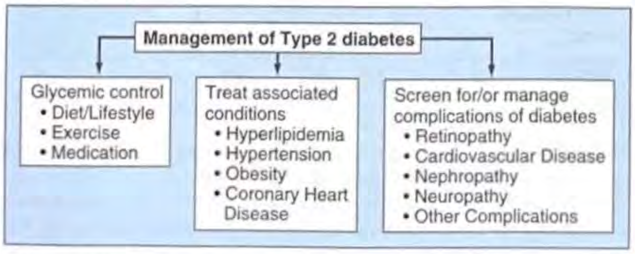

FIGURE 333-13 Essential elements in comprehensive diabetes care of type 2 diabetes.

Insulin secretagogues are well tolerated in general. All of these agents, however, have the potential to cause profound and persistent hypoglycemia, especially in elderly individuals. Hypoglycemia is usually related to delayed meals, increased physical activity, alcohol intake, or renal insufficiency. Individuals who ingest an overdose of these agents develop prolonged and serious hypoglycemia and should be monitored closely in the hospital (Chap. 334). Most sulfonylureas are metabolized in the liver to compounds that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable. Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control. Some sulfonylureas have significant drug interactions with other medications such as alcohol, warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole. Despite prior concerns that use of sulfonylureas might increase cardiovascular risk, recent trials have refuted this claim.

BIGUANIDES Metformin is representative of this class of agents. It reduces hepatic glucose production through an undefined mechanism and may improve peripheral glucose utilization slightly (Table 333-12). Metformin reduces fasting plasma glucose and insulin levels, improves the lipid profile, and promotes modest weight loss. The initial starting dose of 500 mg once or twice a day can be increased to 850 mg tid or 1000 mg bid. Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be escalated every 2 to 3 weeks based on SMBG measurements. The major toxicity of metformin, lactic acidosis, can be prevented by careful patient selection. Metformin should not be used in patients with renal insufficiency [serum creatinine >133 μmol/L (1.5 mg/dL) in men or >124 μmol/L (1.4 mg/dL) in women, with adjustments for age], any form of acidosis, congestive heart failure, liver disease, or severe hypoxia. Metformin should be discontinued in patients who are seriously ill, in patients who can take nothing orally, and in those receiving radiographic contrast material. Insulin should be used until metformin can be restarted. Though well tolerated in general, some individuals develop gastrointestinal side effects (diarrhea, anorexia, nausea, and metallic taste) that can be minimized by gradual dose escalation. Because the drug is metabolized in the liver, it should not be used in patients with liver disease or heavy ethanol intake.

α-GLUCOSIDASE INHIBITORS α-Glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion (Table 333-12). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen. Therapy should be initiated at a low dose (25 mg of acarbose or miglitol) with the evening meal and may be increased to a maximal dose over weeks to months (50 to 100 mg for acarbose or 50 mg for miglitol with each meal). The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward dose titration. α-Glucosidase inhibitors may increase levels of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2.0 mg/dL). This class of agents is not as potent as other oral agents in lowering the HbA1c but is unique in that it reduces the postprandial glucose rise even in individuals with type 1 DM.

THIAZOLIDINEDIONES Thiazolidinediones represent a new class of agents that reduce insulin resistance. These drugs bind to a nuclear receptor (peroxisome proliferator-activated receptor, PPAR-γ) that regulates gene transcription. The PPAR-γ receptor is found at highest

Table 333-12 Oral Glucose-Lowering Therapies in Type 2 DM

	Mechanism of Action	Examples	Anticipated Reduction in HbA1c, %	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications
Insulin secretagogues	↑ Insulin		1–2			
Sulfonylureas		See Table 333-13		Lower fasting blood glucose	Hypoglycemia weight gain, hyperinsulinemia	Renal/liver disease
Meglitinide		Repaglinide		Short onset of action, lower postprandial glucose	Hypoglycemia	Liver disease
Biguanides	↓ Hepatic glucose production, weight loss, ↑ glucose utilization	Metformin	1–2	Weight loss, improved lipid profile, no hypoglycemia	Lactic acidosis, diarrhea, nausea, possible increased cardiovascular mortality	Serum creatinine >1.5 mg/dL (men), >1.4 mg/dL (women), radiographic contrast studies, seriously ill patients, acidosis
α-Glucosidase inhibitors	↓ Glucose absorption	Acarbose, miglitol	0.5–1.0	No risk of hypoglycemia	GI flatulence, ↑ liver function tests	Liver/renal disease
Thiazolidinediones	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, pioglitazone	1–2	↓ Insulin and sulfonylurea requirements, ↓ triglycerides	Frequent hepatic monitoring for idiosyncratic hepatocellular injury (see text)	Liver disease, congestive heart failure
Medical nutrition therapy and physical activity	↓ Insulin resistance	Low-calorie, low-fat diet, exercise	1–2	Other health benefits	Compliance difficult, long-term success low	

levels in adipocytes but is expressed at lower levels in many other insulin-sensitive tissues. Agonists of this receptor promote adipocyte differentiation and may reduce insulin resistance in skeletal muscle indirectly. Thiazolidinediones reduce the fasting plasma glucose by improving peripheral glucose utilization and insulin sensitivity (Table 333-12). Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance. Although direct comparisons are not available, the two currently available thiazolidinediones appear to have similar efficacy; the therapeutic range for pioglitazone is 15 to 45 mg/d in a single daily dose and for rosiglitazone is 2 to 8 mg/d—once a day at lower doses and bid at higher doses. The ability of thiazolidinediones to influence other features of the insulin resistance syndrome is under investigation.

The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure. The two other thiazolidinediones, rosiglitazone and pioglitazone, thus far do not appear to induce the liver abnormalities seen with troglitazone. However, long-term experience with the newer agents is limited. Consequently, the FDA recommends measurement of liver function tests prior to initiating therapy with a thiazolidinedione and at regular intervals (every two months for the first year and then periodically). The thiazolidinediones raise LDL and HDL slightly and lower triglycerides by 10 to 15%, but the clinical significance of these changes is not known. Thiazolidinediones are associated with minor weight gain (1 to 2 kg), a small reduction in the hematocrit, and a mild increase in plasma volume. Cardiac function is not affected, but the incidence of peripheral edema is increased. They are contraindicated in patients with liver disease or congestive heart failure (class III or IV). Thiazolidinediones have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome (see "Insulin Resistance Syndromes," above). Women should be warned about the risk of pregnancy, since the safety of thiazolidinediones in pregnancy is not established.

Table 333-13 Characteristics of Agents that Increase Insulin Secretion

Generic Name	Approved Daily Dosage Range, mg	Duration of Action, h	Clearance
Sulfonylurea			
First generation			
Chlorpropamide	100–500	>48	Renal
Tolazamide	100–1000	12–24	Hepatic, renal
Tolbutamide	500–3000	6–12	Hepatic
Second generation			
Glimepiride	1–8	24	Hepatic, renal
Glipizide	2.5–40	12–18	Hepatic
Glipizide (extended release)	5–10	24	Hepatic
Glyburide	1.25–20	12–24	Hepatic, renal
Glyburide (micronized)	0.75–12	12–24	Hepatic, renal
Meglitinide			
Repaglinide	0.5–16	2–6	Hepatic

SOURCE: Adapted from Zimmerman, 1998.

INSULIN THERAPY IN TYPE 2 DM Modest doses of insulin are quite efficacious in controlling hyperglycemia in newly diagnosed type 2 DM. Insulin should be considered as the initial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic disease that precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes.

Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of intermediate-acting insulin (0.3 to 0.4 U/

kg per day), given either before breakfast or just before bedtime (or ultralente at bedtime). Since fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin. Some physicians prefer a relatively low, fixed starting dose of intermediate-acting insulin (~15 to 20 units in the morning and 5 to 10 units at bedtime) to avoid hypoglycemia. The insulin dose may then be adjusted in 10% increments as dictated by SMBG results. Both morning and bedtime intermediate insulin may be used in combination with oral glucose-lowering agents (biguanides, α-glucosidase inhibitors, or thiazolidinediones).

Choice of Initial Glucose-Lowering Agent Though insulin is an effective primary therapy for type 2 DM, most patients and physicians currently prefer oral glucose-lowering drugs as the initial pharmacologic approach. The level of hyperglycemia should influence the initial choice of therapy. Assuming maximal benefit of MNT and increased physical activity has been realized, patients with mild to moderate hyperglycemia [fasting plasma glucose <11.1 to 13.9 mmol/L (200 to 250 mg/dL)] often respond well to a single oral glucose-lowering agent. Patients with more severe hyperglycemia [fasting plasma glucose >13.9 mmol/L (250 mg/dL)] may respond partially but are unlikely to achieve normoglycemia with oral monotherapy. Nevertheless, many physicians prefer a stepwise approach that starts with a single agent and adds a second agent to achieve the glycemic target (see "Combination Therapy," below). Some physicians begin insulin in individuals with severe hyperglycemia [fasting plasma glucose >13.9 to 16.7 mmol/L (250 to 300 mg/dL)]. This approach is based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, improve endogenous insulin secretion, and possibly allow oral glucose-lowering agents to be more effective. If this occurs, the insulin may be discontinued.

Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has unique advantages and disadvantages, certain generalizations apply: (1) insulin secretagogues, biguanides, and thiazolidinediones improve glycemic control to a similar degree (1 to 2% reduction in HbA1c) and are more effective than α-glucosidase inhibitors; (2) assuming a similar degree of glycemic improvement, no clinical advantage to one class of drugs has been demonstrated, and any therapy that improves glycemic control is beneficial; (3) insulin secretagogues and α-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by several weeks to months; (4) not all agents are effective in all individuals with type 2 DM (primary failure); (5) biguanides, α-glucosidase inhibitors, and thiazolidinediones do not directly cause hypoglycemia; and (6) most individuals will eventually require treatment with more than one class of oral glucose-lowering agents, reflecting the progressive nature of type 2 DM.

Considerable clinical experience exists with sulfonylureas and metformin because they have been available for several decades. It is assumed that the α-glucosidase inhibitors and thiazolidinediones, which are newer classes of oral glucose-lowering drugs, will reduce DM-related complications by improving glycemic control, although long-term data are not yet available. The thiazolidinediones are theoretically attractive because they target a fundamental abnormality in type 2 DM, namely insulin resistance. However, these agents are currently more costly than others and require liver function monitoring.

A reasonable treatment algorithm for initial therapy proposes either a sulfonylurea or metformin as initial therapy because of their efficacy, known side-effect profile, and relatively low cost (Fig. 333-14). Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, improves the lipid profile slightly, and may have a lower secondary failure rate. However, there is no difference in response rate or degree of glycemic control when metformin and sulfonylureas are compared in randomized, prospective clinical trials. Based on SMBG results and the HbA1c, the dose of either the sulfonylurea or metformin should be increased until the glycemic target is achieved. α-Glucosidase inhibitors and thiazolidinediones are alternative, initial agents (Fig. 333-14).

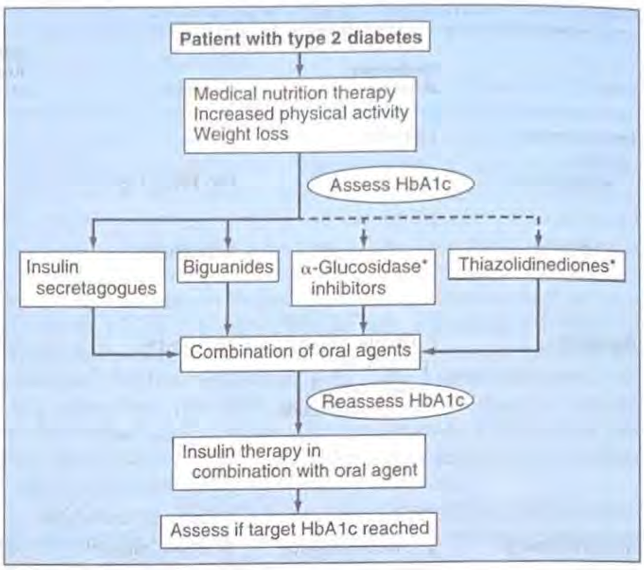
Patient with type 2 diabetes
Medical nutrition therapy
Increased physical activity
Weight loss
Assess HbA1c
Insulin secretagogues
Biguanides
α-Glucosidase* inhibitors
Thiazolidinediones*
Combination of oral agents
Reassess HbA1c
Insulin therapy in combination with oral agent
Assess if target HbA1c reached

FIGURE 333-14 Glycemic management of type 2 diabetes. See text for discussion. *See text about use as monotherapy. The broken line indicates that biguanides or insulin secretagogues, but not α glucosidase inhibitors or thiazolidinediones, are preferred for initial therapy.

When used as monotherapy, approximately one-third of individuals will reach their target glycemic goal with either a sulfonylurea or metformin. Approximately 25% of individuals will not respond to sulfonylureas or metformin; under these circumstances, the drug usually should be discontinued. Some individuals respond to one agent but not the other. The remaining individuals treated with either sulfonylureas or metformin alone will exhibit some improvement in glycemic control but will not achieve their glycemic target and should be considered for combination therapy.

Combination Therapy with Glucose-Lowering Agents A number of combinations of therapeutic agents are successful in type 2 DM, and the dosing of agents in combination is the same as when the agents are used alone. Because mechanisms of action of the first and second agents are different, the effect on glycemic control is usually additive. Commonly used regimens include: (1) insulin secretagogue with metformin or thiazolidinedione, (2) sulfonylurea with α-glucosidase inhibitor, and (3) insulin with metformin or thiazolidinedione. The combination of metformin and a thiazolidinedione is also effective and complementary. If adequate control is not achieved with two oral agents, bedtime insulin or a third oral agent may be added stepwise. However, long-term experience with any triple combination is lacking, and experience with two-drug combinations is relatively limited.

Insulin becomes required as type 2 DM enters the phase of relative insulin deficiency (as seen in long-standing DM) and is signaled by inadequate glycemic control on one or two oral glucose-lowering agents. Insulin can be used in combination with any of the oral agents in patients who fail to reach the glycemic target. For example, a single dose of intermediate-acting insulin at bedtime is effective in combination with metformin. As endogenous insulin production falls further, multiple injections of intermediate-acting and short-acting insulin regimens are necessary to control postprandial glucose excursions. These combination regimens are identical to the intermediate- and short-acting combination regimens discussed above for type 1 DM. Since the hyperglycemia of type 2 DM tends to be more "stable," these regimens can be increased in 10% increments every 2 to 3 days using SMBG results. The daily insulin dose required can become quite large (1 to 2 units/kg per day) as endogenous insulin production falls and insulin resistance persists. Individuals who require >1 unit/kg per day of intermediate-acting insulin should be considered for combination therapy with metformin or a thiazolidinedione. The addition of a thiazolidinedione can reduce insulin requirements in some individuals with type 2 DM, while maintaining or even improving glycemic control.

Intensive diabetes management (Table 333-10) is a treatment option in type 2 patients who cannot achieve optimal glycemic control and are capable of implementing such regimens. A recent study from the Veterans Administration found that intensive diabetes management is not associated with a greater degree of side effects (hypoglycemia, weight gain) than standard insulin therapy. The effect of higher insulin levels associated with intensive diabetes management on the prognosis of diseases commonly associated with type 2 DM (cardiovascular disease, hypertension) is still debated. In selected patients with type 2 DM, insulin pumps improve glycemic control and are well tolerated.

Emerging Therapies Whole pancreas transplantation (conventionally performed concomitantly with a renal transplant) may normalize glucose tolerance and is an important therapeutic option in type 1 diabetes, though it requires substantial expertise and is associated with the side effects of immunosuppression. Pancreatic islet transplantation has been plagued by limitations in pancreatic islet isolation and graft survival, but recent advances in specific immunomodulation have greatly improved the results. Islet transplantation is an area of active clinical investigation.

Advances in molecular biology and new insights into normal mechanisms of glucose homeostasis have led to a number of emerging therapies for diabetes and its complications. For example, glucagon-like peptide 1, a potent insulin secretagogue, may be efficacious in type 2 DM. Inhaled insulin and additional insulin analogues are in advanced stages of clinical trials. Aminoguanidine, an inhibitor of the formation of advanced glycosylation end products, and inhibitors of protein kinase C may reduce the complications of DM. Closed-loop pumps that infuse the appropriate amount of insulin in response to changing glucose levels are potentially feasible now that continuous glucose-monitoring technology has been developed.

COMPLICATIONS OF THERAPY FOR DIABETES MELLITUS

As with any therapy, the benefits of efforts directed towards glycemic control must be weighed against the risks of treatment. Side effects of intensive treatment include an increased frequency of serious hypoglycemia, weight gain, increased economic costs, and greater demands on the patient. In the DCCT, quality of life was very similar in the intensive therapy and standard therapy groups. The most serious complication of therapy for DM is hypoglycemia (Chap. 334). Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin and α-glucosidase inhibitors) therapies that improve glycemic control due to the anabolic effects of insulin and the reduction in glucosuria. In the DCCT, individuals with the greatest weight gain exhibited increases in LDL cholesterol and triglycerides as well as increases in blood pressure (both systolic and diastolic) similar to those seen in individuals with type 2 DM and insulin resistance. These effects could increase the risk of cardiovascular disease in intensively managed patients. As discussed previously, improved glycemic control is sometimes accompanied by a transient worsening of diabetic retinopathy or neuropathy.

ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 333-14). These screening procedures are indicated for all individuals with DM, but numerous studies have documented that most individuals with diabetes do not receive comprehensive diabetes care. Screening for dyslipidemia and hypertension should be performed annually. In addition to routine health maintenance, individuals with diabetes should also receive the pneumococcal and tetanus vaccines (at recommended intervals) and the influenza vaccine (annually).

Table 333-14 Guidelines for Ongoing Medical Care for Patients with Diabetes

- Self-monitoring of blood glucose (individualized frequency)
- HbA1c testing (2–4 times/year)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)
- Eye examination (annual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual; see Fig. 333-13)
- Blood pressure measurement (quarterly)
- Lipid profile (annual)

An annual comprehensive eye examination should be performed by a qualified optometrist or ophthalmologist. If abnormalities are detected, further evaluation and treatment require an ophthalmologist skilled in diabetes-related eye disease. Because many individuals with type 2 DM have had asymptomatic diabetes for several years before diagnosis, a consensus panel from the ADA recommends the following ophthalmologic examination schedule: (1) individuals with onset of DM at <29 years should have an initial eye examination within 3 to 5 years of diagnosis, (2) individuals with onset of DM at >30 years should have an initial eye examination at the time of diabetes diagnosis, and (3) women with DM who are contemplating pregnancy should have an eye examination prior to conception and during the first trimester.

An annual foot examination should: (1) assess blood flow, sensation, and nail care; (2) look for the presence of foot deformities such as hammer or claw toes and Charcot foot; and (3) identify sites of potential ulceration. Calluses and nail deformities should be treated by a podiatrist; the patient should be discouraged from self-care of even minor foot problems.

An annual microalbuminuria measurement is advised in individuals with type 1 or type 2 DM and no protein on a routine urinalysis (Fig. 333-10). If the urinalysis detects proteinuria, the amount of protein should be quantified by standard urine protein measurements. If the urinalysis was negative for protein in the past, microalbuminuria should be the annual screening examination. Routine urine protein measurements do not detect low levels of albumin excretion. Screening should commence 5 years after the onset of type 1 DM and at the time of onset of type 2 DM.

SPECIAL CONSIDERATIONS IN DIABETES MELLITUS

PSYCHOSOCIAL ASPECTS As with any chronic, debilitating disease, the individual with DM faces a series of challenges that affect all aspects of daily life. The individual with DM must accept that he or she may develop complications related to DM. Even with considerable effort, normoglycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. The patient should view him- or herself as an essential member of the diabetes care team and not as someone who is cared for by the diabetes team. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. This can lead to the appearance of either hyper- or hypoglycemia. Depression and eating disorders (in women) are more common in individuals with type 1 or type 2 DM (Chap. 78).

MANAGEMENT IN THE HOSPITALIZED PATIENT Virtually all medical and surgical subspecialties may be involved in the care of hospitalized patients with diabetes. General anesthesia, surgery, and concurrent illness raise the levels of counterregulatory hormones (cortisol, growth hormone, catecholamines, and glucagon), and infection may lead to transient insulin resistance. These factors increase insulin requirements by increasing glucose production and impairing glucose utilization and thus may worsen glycemic control. On the other hand, the concurrent illness or surgical procedure may prevent the patient with DM from eating normally and may promote hypoglycemia. Glycemic control should be assessed (with HbA1c) and, if feasible, should be optimized prior to surgery. Electrolytes, renal function, and intravascular volume status should be assessed as well. The extremely high prevalence of asymptomatic cardiovascular disease in individuals with DM (especially in type 2 DM) may require preoperative cardiovascular evaluation.

The goals of diabetes management during hospitalization are avoidance of hypoglycemia, optimization of glycemic control, and transition back to the outpatient diabetes treatment regimen. Attention to each stage in this process requires integrating information regarding the plasma glucose, diabetes treatment regimen, and clinical status of the patient. For example, some surgical procedures utilizing local anesthesia or epidural anesthesia may have minimal effects on glycemic control. If the patient is eating soon after the procedure and there is no disruption of the patient's regular meal plans, then glycemic control is usually maintained.

The physician caring for an individual with diabetes in the perioperative period, during times of infection or serious physical illness, or simply when fasting for a diagnostic procedure must monitor the plasma glucose vigilantly, adjust the diabetes treatment regimen, and provide glucose infusion as needed. Several different treatment regimens (intravenous or subcutaneous insulin regimens) can be employed successfully. Individuals with type 1 DM require continued insulin administration to maintain the levels of circulating insulin necessary to prevent DKA. Prolongation of a surgical procedure or delay in the recovery room is not uncommon and may result in periods of insulin deficiency. Even relatively brief periods without insulin may lead to mild DKA. Individuals with type 1 DM who are undergoing general anesthesia and surgery, or who are seriously ill, should receive continuous insulin, either through an intravenous insulin infusion or by subcutaneous administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient.

Individuals with type 2 DM can be managed with either insulin infusion or a reduced dose of subcutaneous insulin. Oral glucose-lowering agents are discontinued at the time a combined insulin/glucose infusion is started. Oral agents such as sulfonylureas, metformin, acarbose, and thiazolidinediones are not useful in regulating the plasma glucose in clinical situations where the insulin requirements and glucose intake are changing rapidly. Moreover, these oral agents may be dangerous if the patient is fasting (e.g., hypoglycemia with sulfonylureas). Metformin should be withheld when radiographic contrast media will be given or if severe congestive heart failure, acidosis, or declining renal function is present.

Insulin infusions can effectively control plasma glucose in the perioperative period and when the patient is unable to take anything by mouth. The absorption of subcutaneous insulin may be variable in such situations because of changes in blood flow. The physician must consider carefully the clinical setting in which an insulin infusion will be utilized, including whether adequate ancillary personnel are available to monitor the plasma glucose frequently and whether they can adjust the insulin infusion rate, either based on an algorithm or in consultation with the physician. The initial rate for an insulin infusion may range from 0.5 to 5 units/h, depending on the degree of insulin resistance and the clinical situation. Based on hourly capillary glucose measurements, the insulin infusion rate is adjusted to maintain the plasma glucose within the desired range [5.6 to 11.1 mmol/L (100 to 200 mg/dL)]. Glucose infusion, initiated at the time the patient begins fasting, should be adjusted to deliver the equivalent of 50 to 150 mL of D_5W/h until the patient is reliably taking nutrition orally. The insulin infusion can be temporarily discontinued if hypoglycemia occurs and may be resumed at a lower infusion rate once the plasma glucose exceeds 5.6 mmol/L (100 mg/dL).

Insulin infusion is the preferred method for managing patients with type 1 DM in the perioperative period or when serious concurrent illness is present. Individuals with type 2 DM can be managed with an insulin infusion, but subcutaneous insulin in reduced doses can be used effectively as well. If the diagnostic or surgical procedure is brief and performed under local or regional anesthesia, a reduced dose of subcutaneous, long-acting insulin may suffice. This approach facilitates the transition back to the long-acting insulin after the procedure. The dose of long-acting insulin should be reduced by 30 to 40%, and short-acting insulin is either held or, likewise, reduced by 30 to 40%. Glucose should be infused to prevent hypoglycemia.

Total Parenteral Nutrition (See Chap. 76) Total parenteral nutrition (TPN) greatly increases insulin requirements. In addition, individuals not previously known to have DM may become hyperglycemic during TPN and require insulin treatment. Intravenous insulin infusion is the preferred treatment for hyperglycemia, and rapid titration to the required insulin dose is done most efficiently using a separate insulin infusion. After the total insulin dose has been determined, insulin may be added directly to the TPN solution. Often, individuals receiving either TPN or enteral nutrition receive their caloric loads continuously and not at "meal times"; consequently, subcutaneous insulin regimens must be adjusted.

GLUCOCORTICOIDS Glucocorticoids increase insulin resistance, decrease glucose utilization, increase hepatic glucose production, and impair insulin secretion. These changes lead to a worsening of glycemic control in individuals with DM and may precipitate diabetes in other individuals ("steroid-induced diabetes"). The effects of glucocorticoids on glucose homeostasis are dose-related, usually reversible, and most pronounced in the postprandial period. If the fasting plasma glucose is near the normal range, oral diabetes agents (sulfonylureas and acarbose) may be sufficient to reduce hyperglycemia. If the fasting plasma glucose >11.1 mmol/L (200 mg/dL), oral agents are usually not efficacious and insulin therapy is required. Short-acting insulin may be required to supplement long-acting insulin in order to control postprandial glucose excursions.

REPRODUCTIVE ISSUES Reproductive capacity in either men or women with DM appears to be normal. Menstrual cycles may be associated with alterations in glycemic control in women with DM. Pregnancy is associated with marked insulin resistance; the increased insulin requirements often precipitate DM and lead to the diagnosis of GDM. Glucose, which at high levels is a teratogen to the developing fetus, readily crosses the placenta, but insulin does not. Thus, hyperglycemia or hypoglycemia from the maternal circulation may stimulate insulin secretion in the fetus. The anabolic and growth effects of insulin may result in macrosomia. GDM complicates approximately 4% of pregnancies in the United States. The incidence of GDM is greatly increased in certain ethnic groups, including African Americans and Hispanic Americans, consistent with a similar increased risk of type 2 DM. Current recommendations advise screening for glucose intolerance between weeks 24 and 28 of pregnancy in women with high risk for GDM (≥25 years; obesity; family history of DM; member of an ethnic group such as Hispanic American, Native American, Asian American, African American, or Pacific Islander). Therapy for GDM is similar to that for individuals with pregnancy-associated diabetes and involves MNT and insulin, if hyperglycemia persists. Oral glucose-lowering agents have not been approved for use during pregnancy. With current practices, the morbidity and mortality of the mother with GDM and the fetus are no different from those in the nondiabetic population. Individuals who develop GDM are at marked increased risk for developing type 2 DM in the future and should be screened periodically for DM. After delivery, glucose homeostasis should be reassessed in the mother. Most individuals with GDM revert to normal glucose tolerance, but some will continue to have overt diabetes or impairment of glucose tolerance. In addition, children of women with GDM appear to be at risk for obesity and glucose intolerance and have an increased risk of diabetes beginning in the later stages of adolescence.

Pregnancy in individuals with known DM requires meticulous planning and adherence to strict treatment regimens. Intensive diabetes management and normalization of the HbA1c are the standard of care for individuals with existing DM who are planning pregnancy. The crucial period of glycemic control is extremely early following fertilization. The risk of fetal malformations is increased 4 to 10 times in individuals with uncontrolled DM at the time of conception. The goals are normal plasma glucose during the preconception period and throughout the periods of organ development in the fetus.

LIPODYSTROPHIC DM (See also Chap. 354) Lipodystrophy, or the loss of subcutaneous fat tissue, may be generalized in certain genetic conditions such as leprechaunism. Generalized lipodystrophy is associated with severe insulin resistance and is often accompanied by acanthosis nigricans and dyslipidemia. Localized lipodystrophy associated with insulin injections has been reduced considerably by the use of human insulin.

Protease Inhibitors and Lipodystrophy Protease inhibitors used in the treatment of HIV disease (Chap. 309) have been associated with a centripetal accumulation of fat (visceral and abdominal area), accumulation of fat in the dorsocervical region, loss of extremity fat, decreased insulin sensitivity (elevations of the fasting insulin level and reduced glucose tolerance on intravenous glucose tolerance testing), and dyslipidemia. Although many aspects of the physical appearance of these individuals resemble Cushing's syndrome, derangements in cortisol secretion have not been found consistently and do not appear to account for this appearance. Although some individuals have IGT, diabetes is not a common feature. The possibility remains that this is related to HIV infection by some undefined mechanism, since some features of the syndrome were observed before the introduction of protease inhibitors. Therapy for HIV-related lipodystrophy is not well established.

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