VI DIABETES MELLITUS

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Definition and Overview

Diabetes mellitus is a metabolic disease characterized by hyperglycemia that results from defects in insulin secretion, insulin action, or both. Important abnormalities in fat and protein metabolism are also present. Nonetheless, the diagnosis still rests upon demonstrating elevated plasma glucose levels. The chronic hyperglycemia of diabetes mellitus is specifically associated with long-term damage, dysfunction, and failure of various organs, especially the retina and lens of the eye, the kidneys, and both somatic and autonomic nervous systems. The heart, arterial system, and microcirculation are also adversely affected.

A variety of pathogenic processes are involved in the development of different forms of diabetes. These processes range from autoimmune destruction of the beta cells of the pancreatic islets with consequent insulin deficiency to mutations in the insulin receptor gene with consequent resistance to insulin action. The basis for the metabolic abnormalities of diabetes mellitus is deficient action of insulin on its major target tissues, including skeletal muscle, cardiac muscle, adipose tissue, and liver. Loss of proper insulin regulation of metabolism results from inadequate secretion of insulin, from diminished tissue responses to insulin at one or more points in the complex pathways of insulin action, or from both processes. Impairment of insulin secretion and defects in insulin action coexist in many patients, and in these patients, it is often unclear which abnormality is the primary cause of the hyperglycemia.

Acute life-threatening consequences of diabetes mellitus are ketoacidosis and nonketotic hyperglycemic hyperosmolar coma. Overtreatment of hyperglycemia can lead to hypoglycemia, which may be severe enough to cause seizures and loss of consciousness. Symptoms of poorly controlled hyperglycemia include polyuria, polydipsia, blurred vision, weight loss, polyphagia, stunting of growth, and vulnerability to infections or susceptibility to a more virulent or chronic course when infected.

Specific long-term complications of diabetes include (l) retinopathy with potential loss of vision, (2) nephropathy leading to end stage renal disease (ESRD), and (3) neuropathy with risk of foot ulcers, amputation, Charcot joints, sexual dysfunction, and potentially disabling dysfunction of the stomach, bowel, and bladder. Numerous mechanisms have been discovered that may mediate the specific tissue damage caused by hyperglycemia. Diabetic patients are also at increased risk for atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular disease. These conditions may be related to hyperglycemia as well as to hypertension and abnormal lipoprotein profiles that are often found in diabetic patients.

Sufficient hyperglycemia to cause pathologic and functional changes in target tissues may be present for some time before clinical symptoms lead to a diagnosis of diabetes in many patients. At an even earlier stage, an incipient abnormality in glucose metabolism can be identified on plasma glucose testing, which indicates that the patient is at considerably increased risk for the full clinical disorder.

Classification

The classification of diabetes mellitus has recently been revised by a task force of the American Diabetes Association that included representation from Europe.[1] Major etiologic classes of the disease, along with more esoteric examples, have been categorized [*see Table 1*]. The vast majority of cases of diabetes mellitus are either type 1 (insulin-dependent) or type 2 (non–insulin-dependent) in an approximate ratio of 1:9.

type 1 and type 2 diabetes mellitus

Type 1 and type 2 diabetes were formerly known as insulin-dependent diabetes mellitus (IDDM) and non–insulin-dependent diabetes mellitus (NIDDM), respectively. This classification was abandoned largely because it was difficult to distinguish patients with IDDM from those patients with NIDDM who eventually required insulin treatment to mitigate hyperglycemia. Physicians, nurses, hospital-record-room personnel, health insurers, and even sometimes researchers were hard put to distinguish between these two forms of diabetes using the old terminology. The new classification, dependent on etiology rather than mode of treatment, puts a greater emphasis on the history and characteristics of the patients to determine the probable etiology and type. Two categories of blood glucose elevation, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), that lie between normal glucose levels and overt diabetes have also been established [*see Impaired Glucose Tolerance, below*].[2]

gestational diabetes mellitus

Gestational diabetes mellitus (GDM) constitutes a separate category for cases of diabetes first detected during pregnancy.[3] When diabetes is detected early in pregnancy, it is likely to be type 1 or type 2 diabetes mellitus that is presenting symptomatically and was probably precipitated or worsened by the pregnant state. Diabetes is commonly detected in the second and third trimester (i.e., in 4% of pregnant women) and is likely to be specific for the pregnant state, to be transient, and to reverse to normal glucose tolerance or to IGT on follow-up oral glucose tolerance testing 6 weeks after delivery. However, GDM is associated with a high risk of future diabetes, especially in women who have IGT post partum or who remain obese.[3] Permanent diabetes will develop in approximately 50% of patients within 10 years of GDM. The greatest importance of any single episode of GDM lies in the risks it poses to the fetus. These risks include intrauterine mortality, neonatal mortality, respiratory distress syndrome, hypoglycemia, hypocalcemia, jaundice, and macrosomia, which can cause trauma such as shoulder dystocia during passage through the birth canal.

secondary forms of diabetes mellitus

Of the categories of secondary diabetes [*see Table 1*], endocrinopathies and drug- or chemical-induced diabetes are noteworthy because they represent instances of diabetes that are potentially reversible if they are recognized and the physician can cure the endocrinopathy or discontinue the offending drug. The category of genetic defects in beta cell function illustrates how the classification will grow ever more detailed as knowledge increases. For example, the single diabetes mellitus phenotype formerly called maturity-onset diabetes of the young (MODY) can now be

more precisely classified into at least four genetic varieties, each of which arises from mutation of a different gene.

Diabetes caused by chronic pancreatitis, pancreatectomy, or occasionally carcinoma of the pancreas is usually type 1 in character. Because patients with this disease have glucagon as well as insulin deficiency, they are somewhat less likely to go into ketoacidosis[4] but are quite vulnerable to hypoglycemia. Because they are deficient in pancreatic enzymes, their digestion and subsequent absorption of nutrients is somewhat erratic, even though replacement enzymes are ingested with meals. If alcoholism, often the cause of chronic pancreatitis, is irremediable, it also contributes to blood glucose instability, as does the often accompanying irregular lifestyle. Small frequent doses of lispro insulin should be helpful, but safety may require less stringent blood glucose goals in such patients.

Although many individual drugs have been incriminated as a cause of hyperglycemia, the continued use of pharmacologic anti-inflammatory or immunosuppressive doses of synthetic glucocorticoids is an especially important continuing problem. Up to 25% of renal transplant patients develop so-called steroid diabetes.[5] In a case-control study, use of glucocorticoids for up to 45 days was a risk factor for diabetes that required pharmacologic treatment.[6] The odds ratio rose from 1.77 at a prednisone equivalent of 10 mg/day to an odds ratio of 10.3 at 30 mg/day. Obesity and family history of diabetes increased the risk of steroid diabetes. Although insulin resistance in the liver and muscle is a well-recognized effect of glucocorticoids, an action on the beta cells to limit the compensatory response to hyperglycemia[7] adds to the diabetogenic effect at higher steroid doses. Patients treated with glucocorticoids for more than a few days need to be warned to watch for and report clinical symptoms of hyperglycemia promptly. Ketoacidosis is rare, but hyperglycemic hyperosmolar nonketotic coma can occur. Insulin treatment is usually necessary for symptomatic patients and for those with a fasting plasma glucose (FPG) level greater than 200 mg/dl, but sulfonylurea drugs are sometimes effective. There is little systematic information on the efficacy of the other oral agents. In most instances, steroid diabetes is transient, but in a minority of cases, diabetes persists even after withdrawal of the glucocorticoids.

Table 1 Etiologic Classification of Diabetes

- Type 1 diabetes mellitus* (β cell destruction, usually leading to absolute insulin deficiency)
  - Immune mediated
  - Idiopathic
- Type 2 diabetes mellitus* (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
- Other specific types of diabetes
  - Genetic defects of β cell function
    - Chromosome 12, HNF-1α (formerly MODY3)
    - Chromosome 7, glucokinase (formerly MODY2)
    - Chromosome 20, HNF-4α (formerly MODY2)
  - Genetic defects in insulin action
    - Type A insulin resistance
  - Disease of the exocrine pancreas
    - Pancreatitis
    - Trauma/pancreatectomy
    - Neoplasia
  - Endocrinopathies
    - Acromegaly
    - Cushing syndrome
    - Glucagonoma
  - Drug- or chemical-induced
    - Nicotinic acid
    - Glucocorticoids
    - Thiazides
  - Infections
    - Congenital rubella
    - Cytomegalovirus
  - Uncommon forms of immune-mediated diabetes
    - Stiff-man syndrome
    - Anti-insulin receptor antibodies
  - Other genetic syndromes associated with diabetes
    - Down syndrome
    - Turner syndrome
    - Friedreich ataxia
    - Myotonic dystrophy
- Gestational diabetes mellitus (GDM)

Note: The list of other specific types of diabetes is not comprehensive. There are many other such syndromes.
*Patients with any form of diabetes may require insulin treatment at some stage of their disease. Such use of insulin does not, of itself, classify the patient.

Screening for Diabetes

Screening for type 1 diabetes mellitus by office glucose testing is currently indicated in high-risk patients. Current American Diabetes Association criteria for office screening of asymptomatic individuals for type 2 diabetes mellitus employ FPG levels.[1] Screening is recommended in all individuals 45 years of age and older at 3-year intervals. Younger individuals should be screened if they are obese (> 120% desirable body weight or a body mass index ≥ 27), have a first-degree relative with diabetes, are members of a high-risk ethnic population (African American, Hispanic American, Native American, Asian American), have delivered a baby weighing more than 9 lb, have previously had GDM, are hypertensive (blood pressure ≥ 140/90 mm Hg), have atherogenic dyslipidemia (high-density lipoprotein [HDL] cholesterol levels ≤ 35 mg/dl or triglyceride levels ≥ 250 mg/dl) or had IFG or IGT on previous testing.[1] Mass indiscriminate public screening is not justified, because there is as yet no proof of population benefit.

Epidemiology

TYPE 1 DIABETES MELLITUS

Available, but not up-to-date, studies suggest the prevalence of type 1 diabetes mellitus in the United States is 1.7 per 1,000 in individuals younger than 19 years and 2.1 per 1,000 in adults.[8] A total prevalence of approximately 500,000 is estimated. Current estimates of annual incidence are 18 per 100,000 population in the 0- to 19-year age range and 9 per 100,000 population in those older than 20 years.[8] Approximately 30,000 cases of type 1 diabetes mellitus are estimated to occur yearly in the United States, and it is more common in whites than in African Americans. Worldwide, the highest annual incidence of type 1 diabetes mellitus is found in Finland (35 cases per 100,000) and the lowest is found in Korea (< 1 per 100,000).

TYPE 2 DIABETES MELLITUS

Analysis of data from the third National Health and Nutrition Examination Survey (NHANES III), conducted from 1988 to 1994,[9] indicates a prevalence of 5.1% for adults at least 20 years of

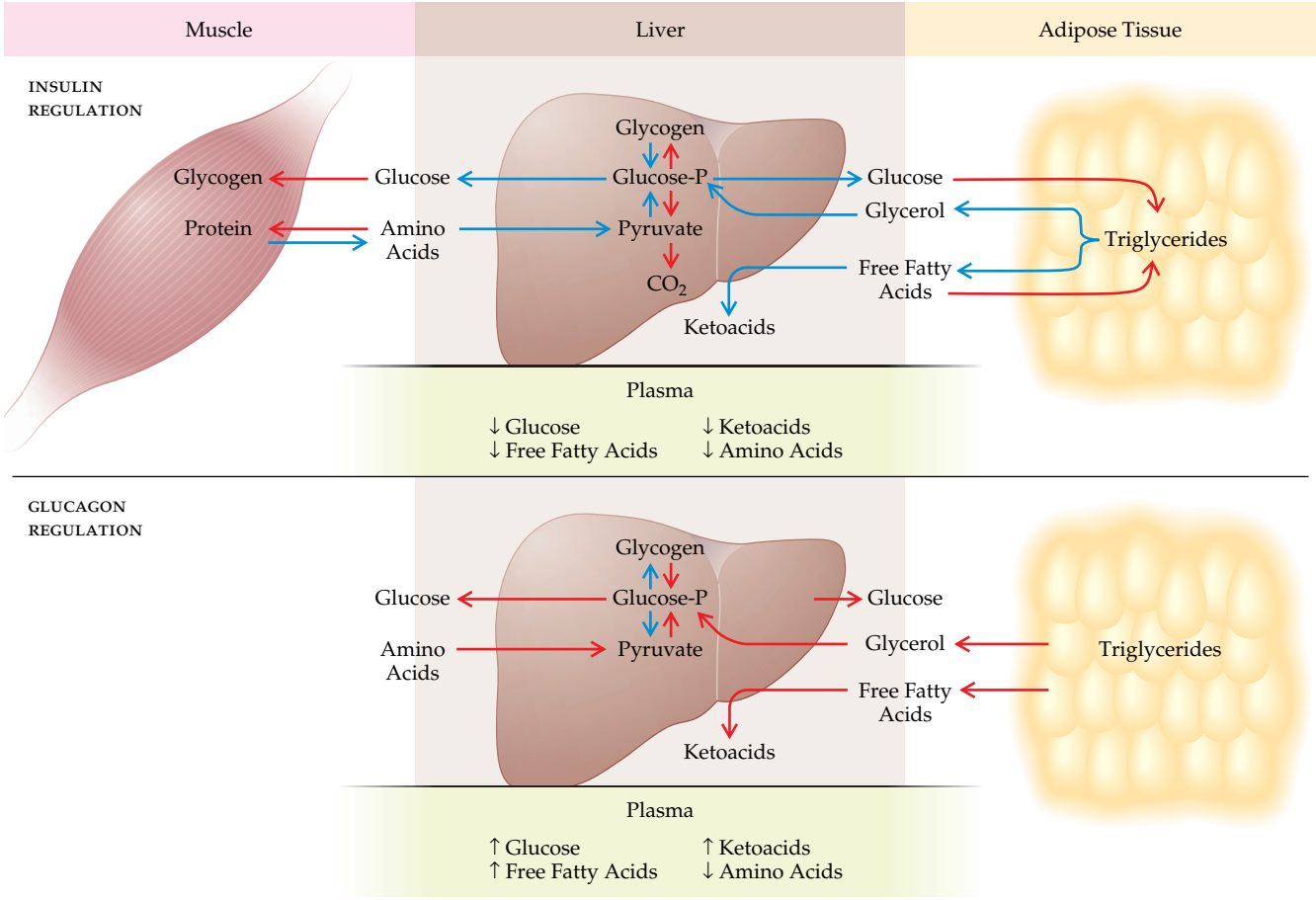


Figure 1 **The opposing actions of insulin and glucagon, particularly within the liver, on substrate flow and plasma levels are seen here. The two hormones have directly opposite effects on key enzymes, such as glycogen synthase and phosphorylase. Thus, stimulatory effects of glucagons on glucose and ketoacid production are magnified when insulin is deficient, as in type 1 diabetes mellitus. Red arrows indicate stimulation. Blue arrows indicate inhibition.**

age in the United States and a prevalence of 2.7% of undiagnosed diabetes (FPG ≥ 126 mg/dl). A prevalence of 12.3% (diagnosed plus undiagnosed) was estimated for individuals 40 to 74 years of age. There are an estimated 10.2 million diagnosed and 5.4 million undiagnosed cases of diabetes in the United States. The estimated number of persons with IGT approximately equals the number with diabetes. Non-Hispanic African-American and Mexican-American women have nearly twice the prevalence of diabetes as non-Hispanic white women. Non-Hispanic African-American men have a slightly higher risk than non-Hispanic white men, but Mexican-American men have about a 50% greater risk than non-Hispanic white men.[9]

Annual incidence of type 2 diabetes mellitus per 100,000 population ranges from 180 in 25 to 44 year olds to a peak of 860 in 65 to 74 year olds. Approximately 625,000 cases of type 2 diabetes mellitus develop yearly in the United States.[10] The prevalence is expected to rise from 15 million in the year 2000 to 21 million in 2025. Worldwide, the prevalence of type 2 diabetes mellitus will likely increase from 150 million to 300 million during that time.[11] The increase[12] reflects aging of the population, strikingly increased obesity,[13] and a sedentary lifestyle. This rise in the number of cases is especially troubling in regard to high-risk ethnic minorities whose access to medical care may be limited.[14,15]

Obesity is a major risk factor for type 2 diabetes mellitus.[16] The current definition of obesity employs the body mass index (BMI) (body weight in kilograms divided by height in meters squared). A person with a BMI of at least 25 but less than 30 is defined as overweight.[17] A BMI of 30 or more is defined as obesity,[16] and a BMI of 40 and above is associated with a 15-fold increased risk of type 2 diabetes mellitus.[15] Abdominal obesity, defined as a waist circumference greater than 100 cm in men and greater than 88 cm in women or a waist-to-hip ratio greater than 0.9, is an especially strong risk factor for type 2 diabetes mellitus. A large preponderance of patients with type 2 diabetes mellitus are obese; even those with normal BMI may have an increased percentage of their body weight accounted for by fat.[18] Longer duration of obesity further increases the risk of diabetes, emphasizing the importance of early efforts to control weight. Many patients with type 2 diabetes mellitus have a strong family history of that disease in first-degree relatives. An extraordinary example is found among the Arizona Pima Indians on the Gila River reservation, where 50% of the adult population has type 2 diabetes mellitus. Other risk factors for the disease include physical inactivity, hypertension, dyslipidemia, gestational diabetes, low birth weight, low income, low level of education, and low socioeconomic status.[1,19]

Hormonal Regulation of Metabolism

Diabetes involves the most fundamental aspects of human metabolism. The following are all affected by the hormonal abnormalities of diabetes: energy production and expenditure; the proportioning of carbohydrate, fat, and protein as energy sourc-

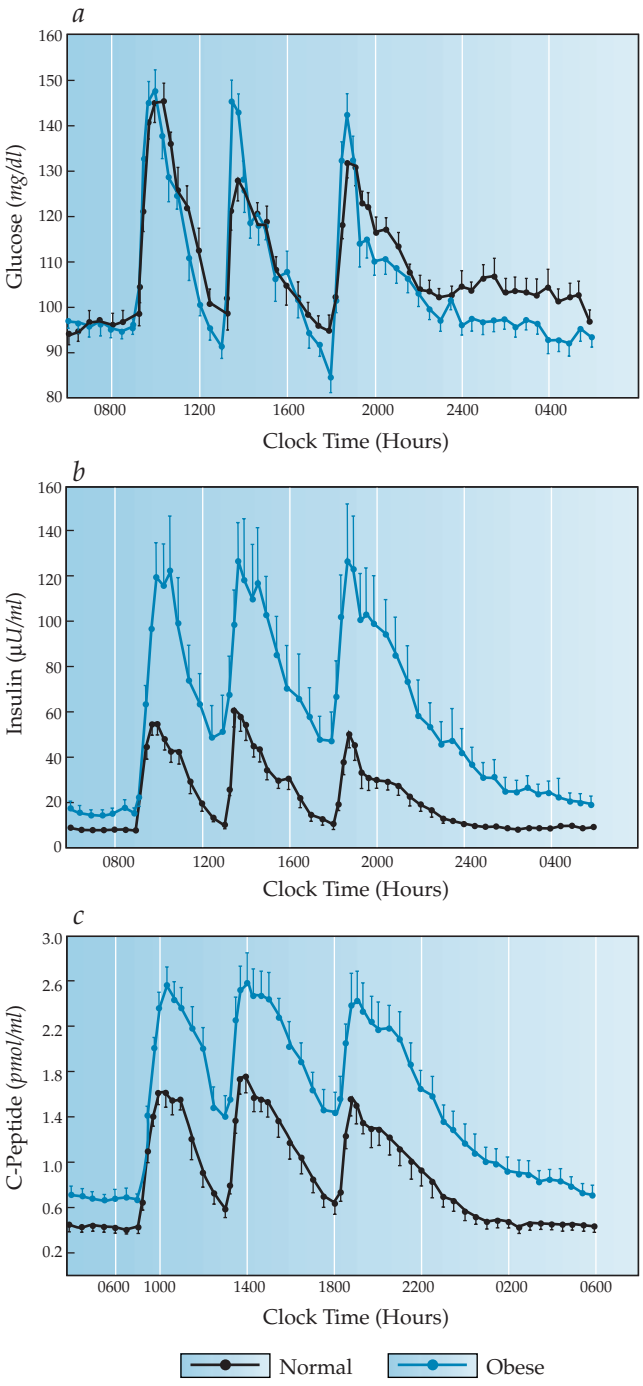


Figure 2 **Plasma glucose (*a*) is normally kept within a narrow range throughout the day, largely because of beta cell function. Plasma insulin (*b*) and plasma C-peptide (*c*) rise sharply from their basal levels with each meal and, after reaching peaks, return promptly to basal levels, which are maintained throughout the night. Note also that plasma insulin and C-peptide levels are elevated in obese individuals who are insulin resistant.**

es; the storage of energy as carbohydrate and fat; and the balance between protein synthesis (anabolism) and degradation (catabolism). To understand the pathogenesis of diabetes, it is useful to start with a brief review of normal metabolism.[20]

A proper balance between insulin and glucagon is one crucial hormonal regulator of basal metabolic homeostasis.[20] Insulin primarily facilitates storage of glucose as glycogen, free fatty acids in triglycerides, and amino acids in protein, and it inhibits glycogenolysis, lipolysis, ketogenesis, proteolysis, and gluconeogenesis [*see Figure 1*]. Glucagon stimulates mobilization of glucose, free fatty acids, and glycerol and stimulates hepatic uptake of amino acids and the conversion of their carbon skeletons to glucose. Glucagon also stimulates ketogenesis from free fatty acids. The normal steady-state levels of insulin and glucagon help maintain the overnight FPG level at 60 to 110 mg/dl, free fatty acid levels at less than 0.7 mmol/L, ketoacids at less than 0.2 mmol/L, and each amino acid at its unique level. After a mixed meal, plasma insulin rises sharply [*see Figure 2*] and, with it, the insulin-glucagon ratio. This condition reverses all the previously described processes. Dietary carbohydrate is stored in muscle and liver glycogen, free fatty acids are reesterified and stored as triglycerides in adipose tissue, and protein metabolism shifts back toward anabolism. When all the nutrients have been assimilated and plasma glucose returns to its basal preprandial level, plasma insulin [*see Figure 2*] and the insulin-glucagon ratio promptly return to basal levels, preventing an overshoot of insulin action that would otherwise cause hypoglycemia. Thus, an immediate rise, an early peak, and a prompt fall in insulin secretion are requisite to normal postprandial metabolism [*see Figure 2*].

Insulin is synthesized in pancreatic islet beta cells from a larger molecule called proinsulin, which is then split to yield insulin and an intramolecular connecting peptide called C-peptide [*see Figure 3*]. The two molecules are stored in the same granules and secreted in an equimolar ratio when the beta cell is stimulated. Thus, plasma C-peptide levels are a faithful marker of beta cell function [*see Figure 3*].

Insulin acts via a plasma insulin receptor that leads to the generation of multiple mediators of insulin's numerous intracellular cytoplasmic and nuclear effects [*see Figure 4*]. Insulin regulates both the activities and syntheses of target enzymes. Sensitivity of target tissues to insulin is the other major determinant of insulin action. Insulin sensitivity is best measured in humans by infusing insulin to establish steady-state plasma insulin levels [*see Figure 5*]. Simultaneously, the baseline plasma glucose is maintained at a constant level by a variable glucose infusion. The amount of glucose required to prevent plasma glucose from decreasing under the effect of insulin is equal to the increased amount of glucose being used per unit time under insulin stimulation (assuming that insulin has completely suppressed hepatic glucose output by the liver). The quantity of glucose used per unit time divided by the plasma insulin level provides an index of whole body sensitivity to insulin in the sphere of glucose metabolism.

A feedback loop exists between insulin responsiveness in target tissues and insulin secretion by beta cells. This relation operates to increase insulin secretion in individuals relatively resistant to insulin action and to decrease insulin release in individuals very sensitive to insulin action. The result is one critical mechanism for maintaining fasting and postprandial plasma glucose levels within narrow normal ranges.

Pathogenesis of Microvascular Complications in Diabetes

A distinctive feature of diabetes—the microvascular complications—were only revealed or commonly appreciated after the introduction of insulin therapy in 1922 allowed patients with type 1 diabetes mellitus to live long enough to experience these complications. It should be borne in mind that the descriptions and pathogenetic sequences presented below reflect a former

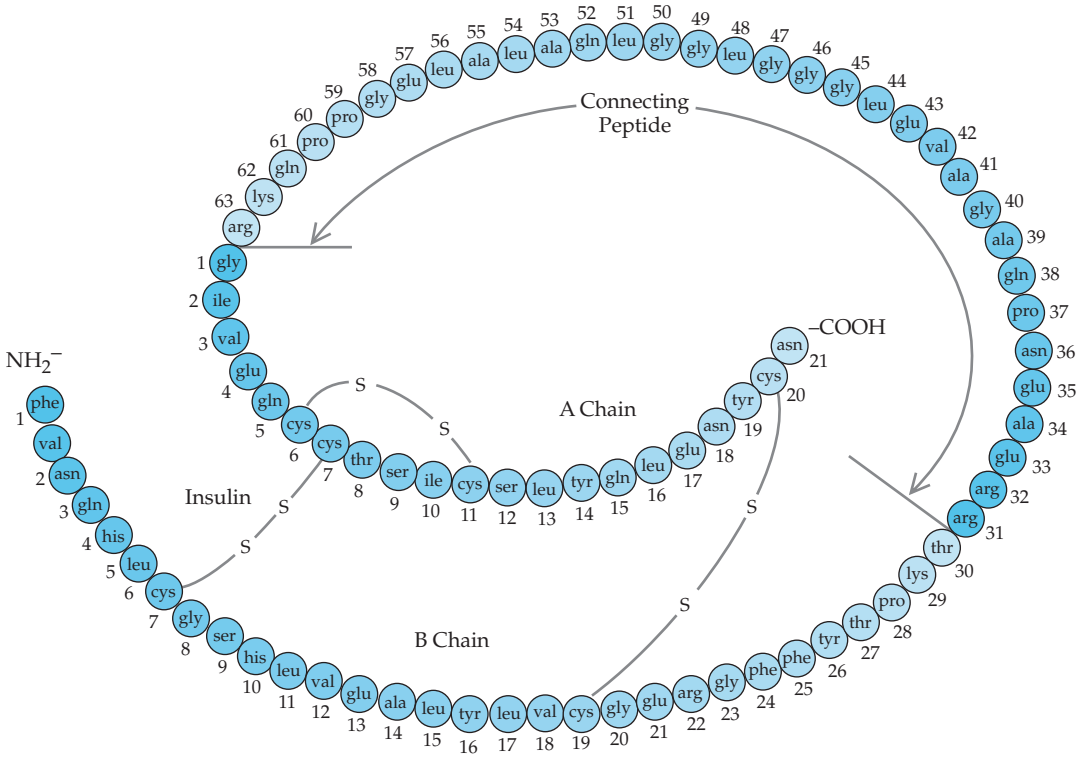


Figure 3 **The structure of human proinsulin, the precursor molecule to insulin. The peptide that connects the amino terminus (NH_2^-) of the A chain to the carboxyl terminus (–COOH) of the B chain is called connecting peptide (C-peptide). Proinsulin is converted to insulin and C-peptide, and these two molecules are packaged together in the secretory granule. On stimulation of the beta cell, C-peptide and insulin are secreted in equimolar proportions. Thus, C-peptide levels reflect beta cell functional capacity.**

commonly practiced degree of metabolic control no longer considered acceptable. Prevention of these complications is a major goal of current therapeutic policy and recommendations for all but transient forms of diabetes [*see* Prevention and Treatment of Microvascular Complications, *below*].

RETINOPATHY

Given a long enough duration, retinopathy occurs in almost all patients with type 1 diabetes mellitus and in most patients with type 2 diabetes mellitus who are on conventional treatment that does not come close to normalizing glycemic levels [*see Table 2*].[21] The most common form of retinopathy is nonproliferative retinopathy (also termed background retinopathy). It begins with loss of capillary pericytes, the supporting cells of the retinal vasculature, a loss leading to capillary dilatations that are seen on direct fundoscopy as microaneurysms [*see Figure 6a*]. Microaneurysms measure 50 to100 µm in diameter and can occur anywhere in the retina. However, they tend to cluster near the macula, the area responsible for central vision and visual acuity. Small dot hemorrhages form when microaneurysms leak blood. Hard lipid exudates form on leakage of serum [*see Figure 6a*]. These lesions are usually benign unless they occur quite close to the macula and in sufficient number to cause clinically significant macular edema. The latter is a feared complication that can decrease central vision and acuity. Capillary closure, which actually begins in the phase of background retinopathy, increases; and in the phase of preproliferative retinopathy, enough capillaries become obstructed to cause ischemia of the retina. Infarctions of the retinal nerve layer appear as soft (cotton wool) exudates. The retina responds to further ischemia with proliferation of new blood vessels from its surface [*see Figure 6b*]. In this phase of proliferative retinopathy, ischemic retina releases vascular endothelial growth factor (VEGF), which stimulates new vessel formation. These new vessels grow forward into the vitreous. They are extremely fragile and can bleed into the vitreous, causing temporary loss of vision until the blood is reabsorbed. If no reabsorption occurs, blindness can result unless successful vitrectomy is carried out. Proliferative vessels that cover more than one fourth of the disk diameter and that occur within 1 disk diameter of the disk [*see Figure 6b*] are especially likely to bleed. Even after reabsorption of the vitreous blood, fibrous scars form that can cause traction on the retina and can lead to retinal detachment, another cause of profound and often permanent loss of vision.

NEPHROPATHY

Diabetic nephropathy [*see Figure 7*] is the complication associated with the highest mortality. Between 35% and 45% of patients with type 1 diabetes mellitus and a somewhat smaller percentage of patients with type 2 diabetes mellitus experience significant nephropathy.[22-24] Histologically, the earliest change is thickening of the capillary basement membrane. Subsequently, mesangial material accumulates diffusely throughout the glomerulus [*see Figure 8*]. Ultimately, there is loss of podocytes and development of peritubular fibrosis. Excretion of low but abnormal levels of albumin in the urine is a marker of the incipient phase of nephropathy.[25] As glomeruli become increasingly filled with mesangial matrix products, albuminuria increases and eventually gross proteinuria appears. Microalbuminuria is defined as excretion of 30 to 300 mg of albumin a day or an albumin-creatinine ratio between 30 and 300 in a random urine spec-

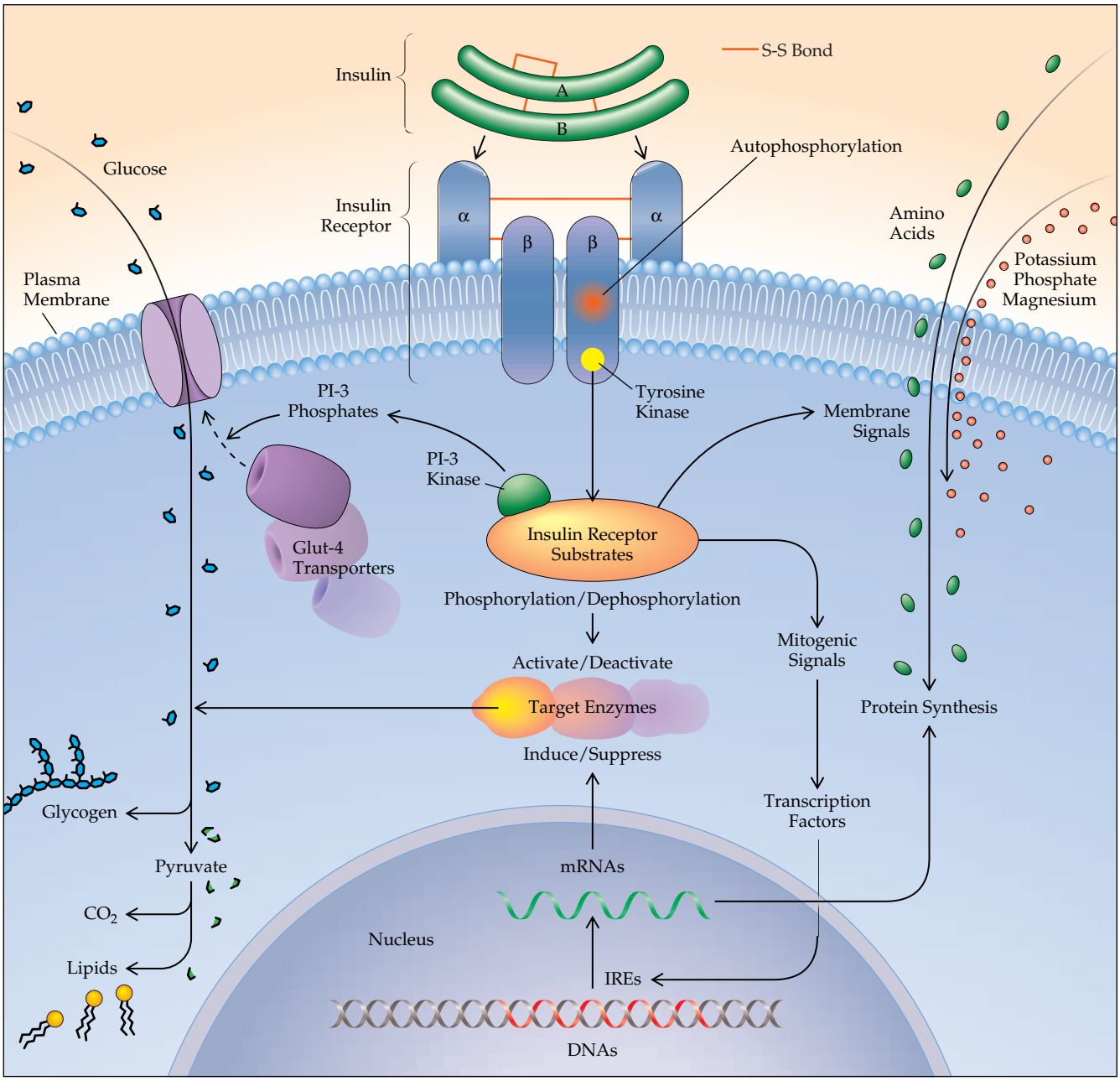


Figure 4 **The cellular actions of insulin begin with binding to its plasma membrane receptor. As a result, certain tyrosine molecules in the intracellular portion of the transmembrane receptor are autophosphorylated, creating tyrosine kinase activity in the receptor. Several intracellular insulin receptor substrates (IRS) are then tyrosine phosphorylated by the receptor. Phosphorylated IRS docks and either activates or inactivates numerous enzymes (e.g., phosphatidylinositol-3-kinase [PI-3 kinase]) and other mediating molecules. Among the chief effects of these insulin-stimulated cascades are translocation of glucose (Glut-4) transporters to the plasma membrane, where they facilitate glucose diffusion into the cell; shifting of intracellular glucose metabolism toward storage as glycogen by activating glycogen synthase; stimulation of cellular uptake of amino acids, phosphate, potassium, and magnesium; stimulation of protein synthesis and inhibition of proteolysis; and regulation of gene expression via insulin regulatory elements (IRE) in target DNA molecules. Numerous intermediates in these various pathways, along with the molecules mentioned above, are products of candidate genes whose mutation could produce the state of insulin resistance characteristic of type 2 diabetes mellitus. Red connectors between insulin chains A and B and among insulin receptor subunits α and β indicate S-S bonds. The A chain also has an intramolecular S-S bond.**

imen. Clinical proteinuria is defined as excretion of more than 0.5 g of total protein a day. This level of excretion can be detected by a positive dipstick urine test for protein. The nephrotic syndrome may also eventually occur.

Early in type 1 diabetes mellitus, kidney size and glomerular filtration rate (GFR) may actually be greater than normal. However, in both types of diabetes, GFR begins to decline, and after clinical proteinuria develops, GFR almost inexorably falls to the level of ESRD [*see Figure 7*]. Unlike the risk of retinopathy, the risk of nephropathy does not continue to rise with increasing duration. The incidence of nephropathy peaks at approximately 15 to 17 years and declines somewhat thereafter.[26] The prevalence of nephropathy remains approximately constant after that time. If the dipstick test has not revealed proteinuria by 25 to 30 years

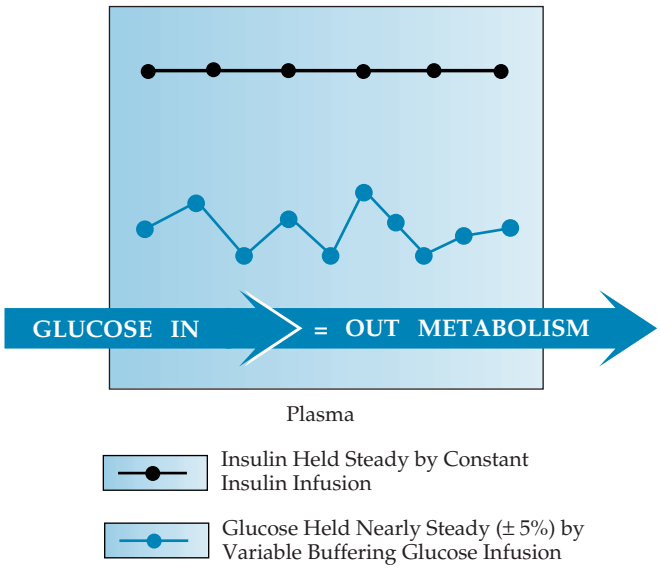


Figure 5 **The diagram represents the gold standard for measuring the sensitivity of glucose metabolism to insulin, utilizing a glucose insulin clamp. When steady state is reached, glucose metabolized/unit time = glucose infused/unit time. Assuming endogenous glucose production is suppressed to zero, insulin sensitivity = (glucose metabolized/unit time) ÷ plasma insulin. For each dose of insulin, the more exogenous glucose required to sustain plasma glucose at its basal levels, the greater the insulin sensitivity. Conversely, individuals who require lesser amounts of glucose than usual to maintain the basal plasma glucose level are insulin resistant. The latter is usually the case in type 2 diabetes mellitus.**

of diabetes duration, the risk of ESRD decreases. Coincident with or shortly after the development of microalbuminuria, hypertension often appears. Hypertension in turn further aggravates diabetic nephropathy and is an important component in the progression to renal failure.

NEUROPATHY

Neuropathy has protean manifestations in diabetes. The most common presentation is peripheral symmetrical sensorimotor neuropathy, which causes numbness or tingling in the toes and feet.[27] At this point, symptoms are only mildly disturbing and require no specific treatment. These symptoms may even abate over time as neuropathy becomes more severe and hypoesthesia or anesthesia takes the place of paresthesias and dysesthesias. Ultimately, insensate feet become very vulnerable to trauma, and neuropathic foot ulcers are frequent causes of hospitalization and even amputation. Testing sensation with a nylon monofilament providing a calibrated 10 g point pressure is an effective way to screen for high risk of foot ulcers. Patients who cannot detect the pressure of the nylon filament have a 30- to 40-fold increased risk of foot ulcer.[28] In some instances, neuropathy is manifested by severe pain that can interfere with sleep and normal daily activities. The distribution of pain can suggest mononeuropathy and radiculopathy. Abrupt onset of cranial neuropathies that most commonly give rise to extraocular muscle weakness and diplopia has been attributed to microinfarcts caused by thrombosis of nutrient blood vessels. Carpal tunnel syndrome and other entrapment syndromes are more frequent in diabetic patients than in nondiabetic patients.

Involvement of the autonomic nervous system is also common and can become debilitating. Manifestations include male impotence and female anorgasmia, difficulty voiding and urinary retention, impaired gastric emptying with early satiety and emesis, diarrhea, orthostatic hypotension, and decreased sweating and vasomotor tone in the lower extremities. The combination of decreased sympathetic tone and loss of vagal control of the heart rate can produce persistent resting sinus tachycardia; sudden death can result.

A form of diabetic neuropathy called amyotrophy occurs most commonly in elderly men with diabetes. It is manifested by severe, unremitting pain and weakness in the thigh muscles. Severe depression, cachexia, and weight loss may mark the 1- to 2-year course of this form of neuropathy. Sometimes confused with painful neuropathy are rare muscle infarcts, usually occurring in the thigh muscles. These infarcts are marked by abrupt onset of severe pain lasting several months. Magnetic resonance imaging of the affected area can demonstrate the presence of necrosis.

Diabetic neuropathy may be another microvascular complication, but the pathogenesis is still not completely understood.[29] Demyelinization of nerves is manifested by decreases in motor and sensory nerve conduction velocities. Axonal degeneration is reflected in decreased amplitudes of action potentials. Histologically, swelling is seen at the axonal nodes. An inflammatory component to diabetic neuropathy has also been suggested.[30]

RELATION OF MICROVASCULAR COMPLICATIONS TO GLYCEMIA

The appearance of microvascular complications in the 1930s generated a 50-year debate about whether diabetic retinopathy, nephropathy, and neuropathy were the direct result of the metabolic abnormalities, most notably hyperglycemia, or whether they were a parallel independent consequence of diabetes that had formerly been usually preempted by death from extreme metabolic disequilibrium (i.e., diabetic coma). This debate ultimately came to encompass type 2 diabetes mellitus as well. The debate was not merely academic, because it was reflected in quite different approaches to treatment. A belief in the metabolic hyperglycemic cause of retinopathy, nephropathy, and neuropathy impelled the physician to work with inadequate means to help the patient achieve as close to normal blood glucose levels as possible. Conversely, a belief in the metabolically independent nature

Table 2 Diabetic Retinopathy

*Stage**	*Pathologic Process*	*Manifestations*
Background	Loss of capillary integrity Leakage, exudation, diapedesis Early capillary closure	Microaneurysms Dot hemorrhages Hard exudates Macular edema
Preproliferative	Capillary closure Microinfarcts Ischemia	Blot hemorrhages Soft exudates Intraretinal microvascular abnormalities Venous beading Macular edema
Proliferative	Forward growth of new large vessels Fibrosis Traction on retina or vitreous	Preretinal hemorrhage Vitreous hemorrhage Retinal detachment Macular edema

*Loss of visual acuity may occur from macular edema at any stage. Blindness may occur from severe macular edema, vitreous hemorrhage, or retinal detachment.

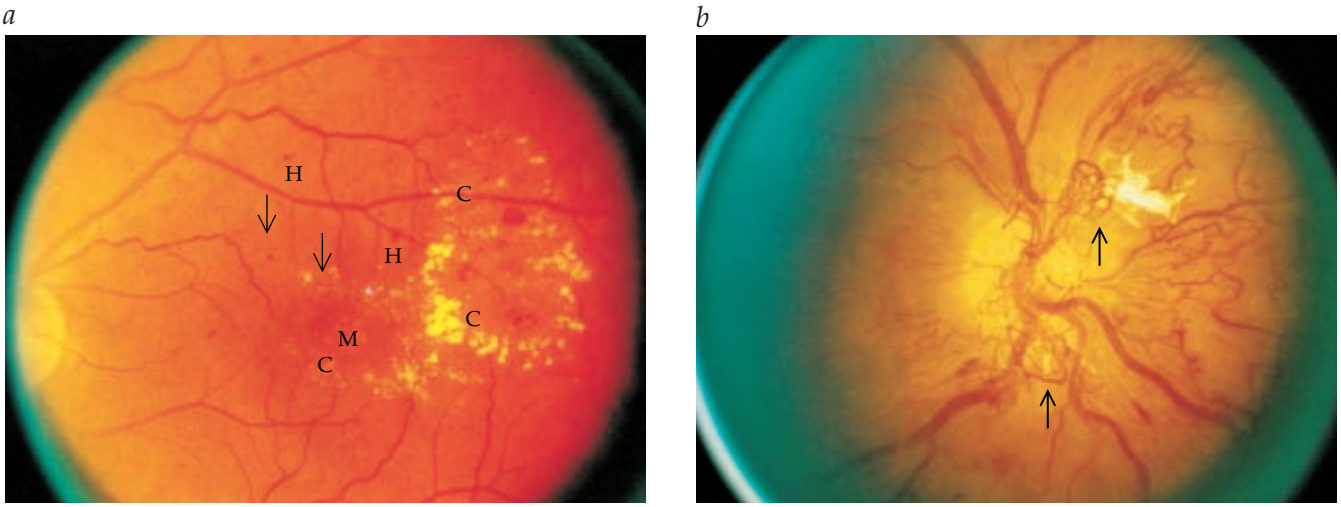


Figure 6 **(*a*) This fundus photograph reveals nonproliferative (or background) retinopathy in a diabetic patient. Microaneurysms (arrows) occur at end capillaries. Punctate (or dot-and-blot) hemorrhages (H) and hard exudates (C) can also be seen. The hard exudates form three distinct circles (termed circinate retinopathy), which indicate leakage of plasma proteins from abnormal vessels located in the centers of the three circles. Lesions in the area of the macula (M) are potentially more dangerous, as they may lead to macular edema requiring laser therapy. (*b*) In proliferative retinopathy, new vessels grow from the retina into the vitreous. This fundus photograph reveals fine, tangled, new vessels originating from several areas of the disk (arrows). The vessels often form arcades and characteristically have thin walls and are fragile. They tend to bleed into the vitreous; the scars that form can cause retinal detachment and loss of vision. Proliferation within one disk diameter of the disk (termed neovascularization of the disk) is particularly dangerous, as these vessels are especially prone to bleed and form traction scars.**

of these complications encouraged a somewhat more laissez-faire approach, which attempted primarily to eliminate the immediate symptoms, such as polyuria, that were produced by plasma glucose levels exceeding the renal threshold (> 180 mg/dl). Furthermore, the risks associated with the more aggressive approach to hyperglycemia reinforced the arguments of the conservative practitioners. A large body of evidence was eventually built up that supported but did not prove the so-called glucose hypothesis.[31] The Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) ended this debate for type 1 and type 2 diabetes mellitus, respectively.

The DCCT[32] was a randomized clinical trial that enrolled 1,441 nonobese patients, aged 13 to 39 years, with type 1 diabetes mellitus. Half of the patients with diabetes of 1 to 5 years' duration participated in a primary prevention trial that excluded all patients with retinopathy or microalbuminuria, and half of the patients with diabetes of 1 to 15 years' duration participated in a secondary intervention trial that included only patients who already had mild to moderate nonproliferative diabetic retinopathy but less than 200 mg/day of urinary albumin excretion. In both of these DCCT trials, patients were randomly assigned either to receive conventional treatment (no more than two insulin injections a day) or to receive intensive treatment (three to four insulin injections a day or use of a continuous subcutaneous insulin infusion [CSII] pump; self-monitoring of blood glucose at least four times a day; premeal target blood glucose levels of 70 to 120 mg/dl; glycated hemoglobin [HbA_{1c}] goal of less than 6.05%; and very frequent contacts between patient and treatment team). An HbA_{1c} difference of 1.8% (8.9% versus 7.1%) was maintained between the two treatment groups for up to 9 years.[33]

Over a mean follow-up of 6.5 years, intensive treatment produced substantial benefits. The risks of de novo development (primary prevention trial) or of progression (secondary intervention trial) of retinopathy were reduced by 27% to 76%; the development of microalbuminuria was reduced by 35%; macroalbu-

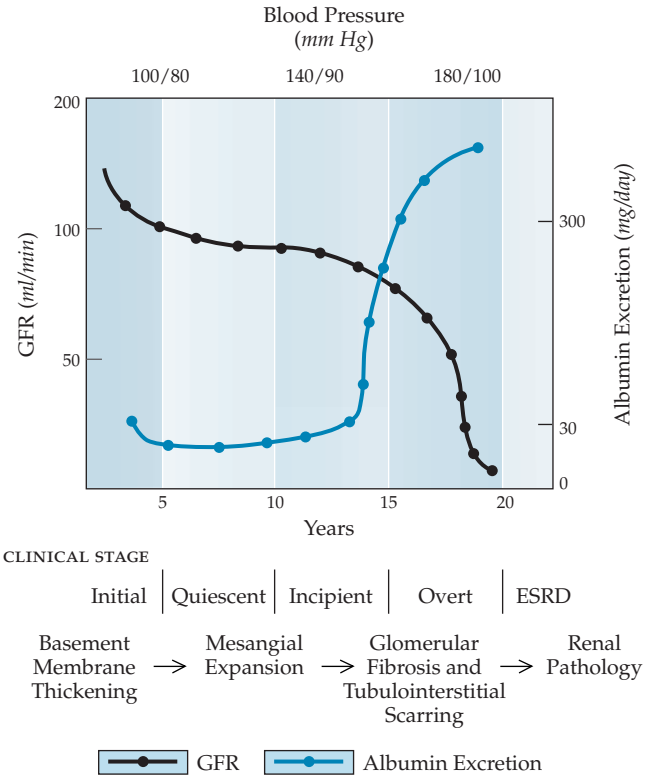
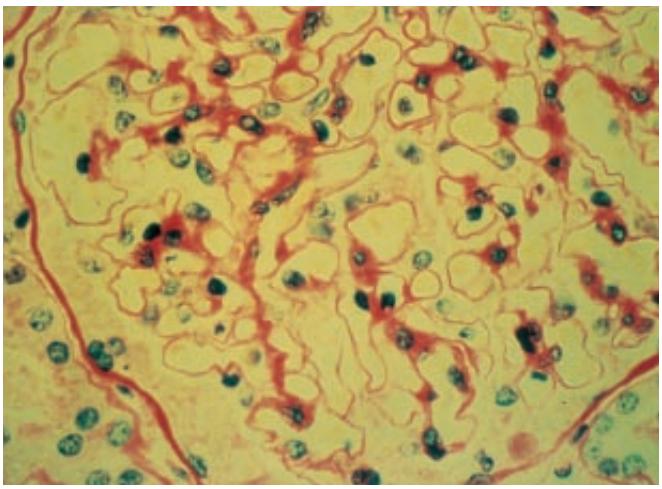


Figure 7 **Relation of the developing histopathologic changes in the kidney to the development of renal functional abnormalities. Note that GFR is actually elevated early, corresponding to early renal hypertrophy. The appearance of microalbuminuria (albumin excretion > 30 mg/day) indicates that the patient is at considerable risk for overt nephropathy and end-stage renal disease (ESRD), but not all such individuals suffer this fate. Blood pressure begins to rise at about the time that microalbuminuria appears, and hypertension further damages the kidney.**

a



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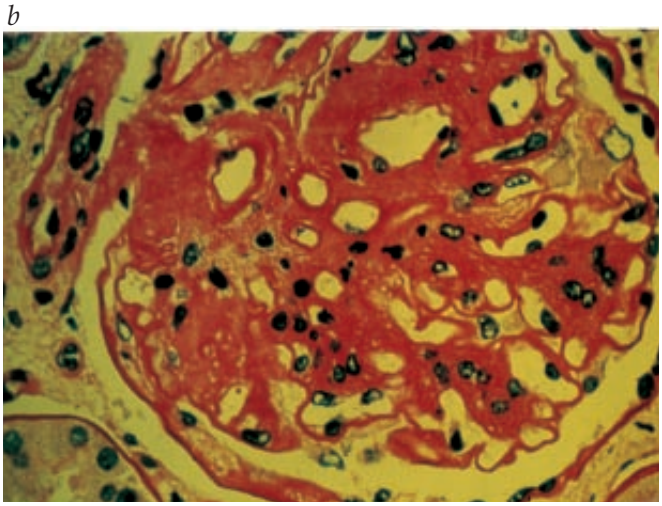

Figure 8 **(*a*) The normal glomerulus with a large filtration surface has a lacy appearance. (*b*) There is diffuse deposition of extramesangial material throughout, as well as thickening of capillary basement membranes in a diabetic glomerulus. The GFR through such a glomerulus is reduced.**

minuria (i.e., proteinuria) was reduced by 56%; and development of clinical neuropathy, confirmed by abnormal nerve conduction velocities or autonomic nervous system function tests, was reduced by 60%.[32] Patients in the primary prevention cohort, with a mean diabetes duration of 2.5 years, had a greater response to intensive treatment than did patients in the secondary prevention cohort, with a mean diabetes duration of 8.5 years.

The main adverse effect of intensive treatment was a threefold increase in the risk of severe hypoglycemic episodes characterized by coma, convulsions, or the required assistance of others to treat and reverse the episode.[32,34] At least one such event per year was experienced by 25% of intensively treated patients, and 50% had experienced more than one such episode by the end of the study[34];14% experienced 10 or more episodes. The overall rate of severe hypoglycemia was 62 events per 100 patient-years for intensive treatment, compared with 19 events per 100 patient-years for conventional treatment. In addition, intensive treatment caused greater weight gain; one third of the patients exceeded 120% of ideal body weight (approximate BMI, 27) by the end of the study.[32] Intensive treatment was also more expensive than conventional treatment.[35] However, the cost was partly offset by projected decreased costs of a lower rate of complications,[36] and the estimated cost per year of quality life gained was $28,661, a figure thought to represent a good value.

The UKPDS[37,38] enrolled 5,102 patients with newly diagnosed type 2 diabetes mellitus, a mean age of 53 years, and a mean BMI of 28. After a 3-month dietary run-in, 1,138 patients were randomly assigned to a continuation of diet treatment only as long as their FPG remained below 270 mg/dl and they had no hyperglycemic symptoms. In the study, 2,729 patients were randomly assigned to intensive treatment, 1,573 to receive one of three sulfonylurea (SU) drugs, and 1,156 to receive insulin. In two thirds of the clinical sites, 342 patients were also randomized to intensive treatment with metformin. The goal of intensive treatment was an FPG of less than 108 mg/dl. Of the conventional-treatment patients, 80% ultimately required drugs to maintain their treatment goals of an FPG of less than 270 mg/dl and freedom from symptoms, although nearly 60% of their total treatment time was spent on diet therapy alone. Likewise, in the intensive-treatment groups, metformin therapy had to be added to the SU therapy, and insulin had to be substituted for or added to oral-drug therapy to maintain the stringent treatment goal.

Despite these drug crossovers, after 10 years of follow-up, patients who received intensive treatment showed a 25% decrease in the risk of serious microvascular complications (vitreous hemorrhage, need for laser treatment, and renal failure), compared with patients given conventional treatment.[37] This important benefit was associated with an HbA_{1c} difference of 0.9% (7.9% for conventional therapy; 7.0% for intensive therapy). Serious hypoglycemia occurred in 3% of insulin-treated patients each year and in 1% to 2% of SU-treated patients. These rates were much lower than that experienced with intensive treatment in patients with type 1 diabetes mellitus in the DCCT.

These two trials provided experimental proof that microvascular and neuropathic complications could be prevented or at least substantially delayed by maintaining blood glucose levels as near to normal as treatment techniques would safely allow. Although these two experimental trials did not prove that hyperglycemia caused microvascular complications, both trials provided additional strong evidence supporting that hypothesis. In the DCCT, the risk of retinopathy was directly related to the preceding mean HbA_{1c} difference in a similar exponential fashion in each of the two treatment groups.[39] The risk of retinopathy was decreased by about 44% for each proportional 10% decrease in HbA_{1c} (e.g., a decrease in HbA_{1c} from 10% to 9.0%). Microalbuminuria and neuropathy showed similar risk relations with glycemia. In the UKPDS, the risk of microvascular complications was also directly related to the mean HbA_{1c} in an exponential fashion.[40] The risk of these complications was decreased by about 37% for every absolute decrease of 1% in HbA_{1c}. These similarities suggest that similar biologic processes are at work. Neither the UKPDS nor the DCCT analyses indicated any glycemic threshold in the diabetic range of HbA_{1c}, below which there was no further risk of microvascular complications.[40,41] This observation sets normoglycemia as the ultimate goal of treating type 1 and type 2 diabetes mellitus. Furthermore, the benefits of previous intensive treatment (or the adverse effects of previous conventional treatment) are still demonstrable 7 years after the DCCT was completed, during which time interval the mean HbA_{1c} concentrations in both groups were nearly identical (approximately 8.0%).[42] Thus, sustained periods of glycemic exposure are associated with pro-

longed consequences. An unacceptable level of hyperglycemia continues to have adverse effects even after some improvement in metabolic control, and a marked reduction in hyperglycemia with intensive treatment continues to have beneficial effects even after some worsening in metabolic control.

Multiple mechanisms by which increased glucose concentrations may cause damage to the retina, kidney, and nerves have been discovered [*see Figure 9*]. (1) Glucose itself can react nonenzymatically with free amino groups in N-terminal amino acids and lysine residues of proteins. $HbA_{1c}$is one such molecule. This reaction sets into motion cross-linking of proteins that ultimately generate harmful advanced glycation end products (AGEs).[43,44] Such products include carboxymethyllysine and pentosidine. Concentrations of long-lived AGEs were higher in tissues of conventionally treated patients in the DCCT than in tissues of intensively treated patients in the DCCT.[45] AGEs correlated with HbA_{1c} and, independent of HbA_{1c}, with the presence of retinopathy, nephropathy, and neuropathy.[45] (2) Three-carbon dicarbonyl products of glucose and lipid metabolism, glyoxal and methylglyoxal, also react readily with amino groups in proteins and produce other AGEs, one of which is argpyrimidine. AGEs react with specific cellular receptors and can stimulate numerous potentially dangerous processes.[43,44] (3) Hyperglycemia can also secondarily produce oxidative stress in tissues, with depletion of glutathione and formation of reactive oxygen species and damaging free radicals.[46] (4) When glucose is insufficiently metabolized by insulin-stimulated routes [*see Figure 1*], it can overflow into the sorbitol (polyol) pathway via the enzymes aldose reductase and sorbitol dehydrogenase.[47] Accumulation of sorbitol and fructose in vulnerable tissues such as nerves produces osmotic damage, loss of myoinositol essential to nerve membrane integrity, and reduction of Na^+, K^+–ATPase activity.[47] (5) Elevated glucose levels increase protein kinase C, an enzyme whose activity influences numerous cellular processes with damaging potential,[48] such as stimulating neovascularization and epithelial cell proliferation, increasing collagen synthesis, increasing vascular permeability, increasing apoptosis (programmed cell death), increasing oxidative stress, and mediating the actions of VEGF and transforming growth factor–β. (6) Elevated glucose levels also increase the production of VEGF, a molecule that stimulates angiogenesis. VEGF is present in high concentrations in human diabetic ocular tissues and in kidneys of animals with experimentally produced diabetes. It is a logical candidate to mediate development of proliferative retinopathy. (7) Hyperglycemia stimulates nitric oxide synthase to produce nitric oxide, a molecule that itself generates damaging free radicals.[46] (8) Excess blood glucose also overflows into the hexosamine pathway, resulting in deleterious products.[49] A single mitochondrial defect that leads to overproduction of reactive oxygen species can result in at least three of the above pathways and has been proposed as the primary culprit.[50] A number of these pathways are also mutually reinforcing, setting up vicious circles that can accelerate tissue damage.

The therapeutic importance of elucidating the mechanistic links between hyperglycemia and microvascular/neuropathic complications lies in our current inability to normalize blood glucose consistently. Therefore, drug therapies that intercept pathogenetic processes downstream from glucose hold promise for preventing these complications, even in the presence of hyperglycemia. An inhibitor of AGE formation, aminoguanidine, has been successful in animal experiments, but human trials

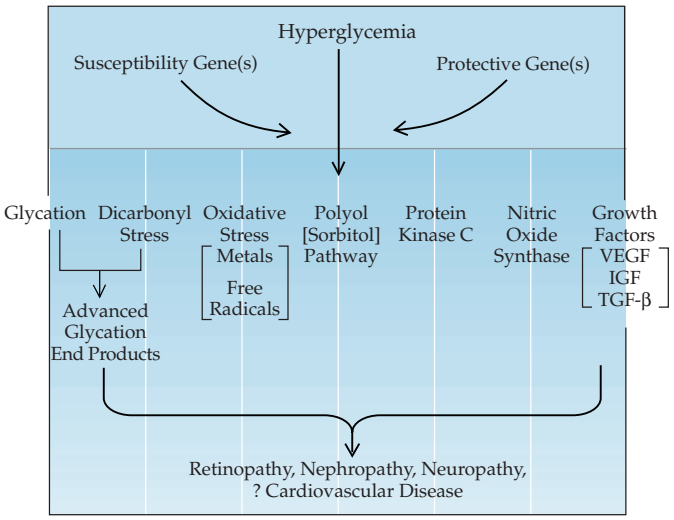

Figure 9 **Multiple pathways have been described that may link high blood glucose levels to the microvascular and neuropathic complications of diabetes (see text). There are good reasons to believe that genetic factors, possibly operating through such pathways, may explain the observation that some individuals with consistently high blood glucose levels do not experience complications, whereas other individuals with near-normal blood glucose levels do experience complications.**

have revealed unacceptable toxicity. Several inhibitors of aldose reductase, catalyzing the first step in the polyol pathway, have been studied in clinical trials, but none have shown sufficient clinical benefit or an acceptable adverse-effect profile to warrant approval in the United States. Nonetheless, such drugs have been effective in animal models. Current clinical trials are testing the effects of antioxidants such as vitamin E and a relatively nontoxic oral inhibitor of protein kinase C. Antagonists to VEGF and other growth factors to be administered by systemic or local injection are also in development.

GENETICS OF MICROVASCULAR COMPLICATIONS

There is considerable evidence from several studies that diabetic nephropathy clusters in families.[51] Thus, either genetic susceptibility or genetic protection is likely to explain the fact that nephropathy develops in only 35% to 40% of patients with diabetes. One likely influence on the development of nephropathy is the family of genes that code for the components of the renin-angiotensin system. Both positive and negative findings have been reported concerning involvement of the gene for angiotensin-converting enzyme (ACE) and the gene for angiotensinogen in the risks for nephropathy and retinopathy. A family study conducted in the DCCT showed no evidence for familial clustering of diabetic retinopathy per se. In view of the nearly 100% prevalence of retinopathy in patients with type 1 diabetes mellitus of many years' duration, it is not likely that a genetic factor is involved in the initiation of retinopathy. The DCCT analyses did, however, show evidence of familial clustering of severe diabetic retinopathy and confirmed familial clustering of nephropathy.[52]

Type 1 Diabetes Mellitus

PATHOGENESIS OF TYPE 1 DIABETES MELLITUS

Type 1 diabetes mellitus is characterized by absolute insulin deficiency, making patients dependent on exogenous insulin re-

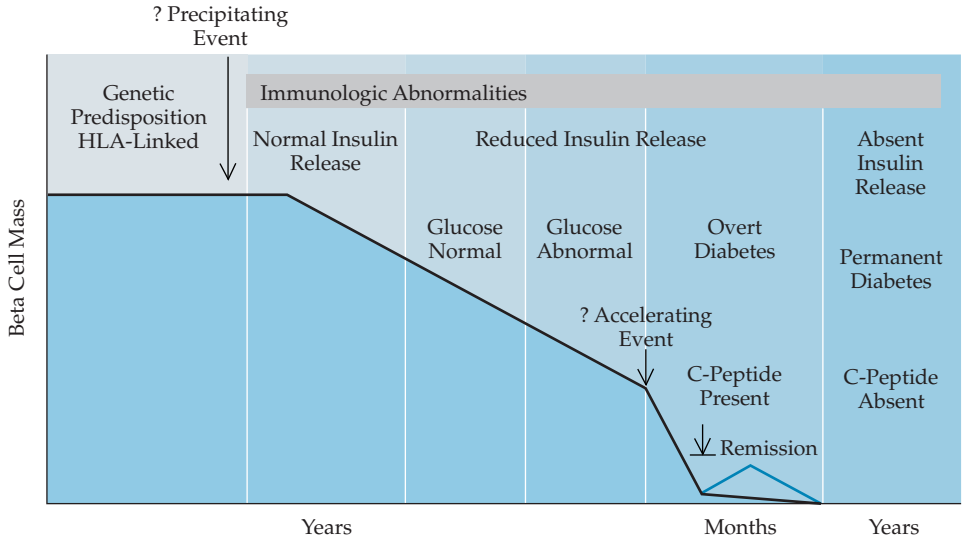

Figure 10 **Current view of the pathogenesis of type 1 autoimmune diabetes mellitus. In some individuals, HLA-linked genes set in motion an autoimmune attack on islet cells, predominantly beta cells. In other individuals, HLA-linked genes protect against the autoimmune destructive response. An initiating event, such as exposure to a virus with an antigenic epitope that resembles a beta cell antigen or to a toxin, may start the process of self-destruction. Disappearance of the beta cells may occur because the viral antigen accelerates the normal rate of apoptosis (programmed cell death). As time passes, insulin production and secretion diminish, despite increasing hyperglycemia. When insulin release falls to trivial amounts or none, diabetic ketoacidosis results. Another external event may trigger this final beta cell catastrophe. A few beta cells may survive, because after this, a brief period of remission marked by reappearance of C-peptide in plasma may ensue if plasma glucose levels are controlled very tightly with exogenous insulin. Eventually, all beta cell function ceases, leading to metabolic instability.**

placement for survival.[53] Insulin deficiency results from destruction or disappearance of the insulin-producing beta cells[54] that constitute 80% of the pancreatic islets of Langerhans. When 90% of the beta cells have been eliminated, clinical diabetes occurs [*see Figure 10*].

Autoimmune Factors

There is strong evidence for a cell-mediated autoimmune process being involved in the destruction of beta cells in the majority of cases of type 1 diabetes mellitus.[55-57] In a number of cases in which death occurred from an accident or from an illness other than diabetes shortly after diagnosis of type 1 diabetes mellitus, a mononuclear lymphocytic infiltrate was found in the islets. In this form of insulinitis, T cell distribution shows an increase in CD8 suppressor-inducer T cells and a decrease in CD4 helper-inducer T cells.[55] A similar immunocellular response has been found in animal models of spontaneous insulin-deficient diabetes.[57] In some instances, experimental manipulations that prevent T cell lymphocytic responses also prevent the development of diabetes. Furthermore, transfer of diabetes from affected animals to nonaffected animals by lymphocytes has also been described. Interleukins and other cytokines have been shown to exhibit toxic effects on the beta cells and to inhibit insulin secretion.

Autoantibodies to a variety of beta cell and islet autoantigens are present in the sera of patients with type 1 diabetes mellitus at the time of diagnosis.[58] The autoantigens include the enzymes glutamic acid decarboxylase (GAD), carboxypeptidase H, a protein tyrosine phosphatase labeled ICA512 or IA-2, and insulin itself.[58-60] Some, but not all, studies have shown that islet autoantibodies are capable of inhibiting insulin secretion in vitro or even causing lysis of beta cells. Other evidence supports the importance of autoimmune phenomena in the pathogenesis of type 1 diabetes mellitus. In cases of transplantation of pancreases from nondiabetic identical twins to patients with type 1 diabetes mellitus who were not given immunosuppressive therapy, the pancreas was rejected by the diabetic host's immune system, which apparently recognized as self, identical antigens in the normal twin's pancreatic islets. If treatment of type 1 diabetes mellitus with the immunosuppressive agent cyclosporine is initiated within 2 to 6 weeks after clinical onset of diabetes, dependency upon insulin can be eliminated or insulin doses markedly reduced, but only as long as immunosuppression is maintained.[61,62] The toxicity associated with cyclosporine and other immunosuppressive agents has precluded use of this form of therapy in clinical practice.

It is now clear that the autoimmune phenomena begin long before clinical onset of the disease. Islet or beta cell autoantibodies can be found in 2% to 4% of first-degree relatives of patients with type 1 diabetes mellitus, which is 10 to 20 times the prevalence of control subjects. Longitudinal studies have shown that type 1 diabetes mellitus is much more likely to develop in clinically unaffected relatives with high autoantibody titers than in relatives without such antibodies, and that the disease will develop in such patients within a few years.[63-65] Longitudinal serial testing of plasma insulin responses to intravenous glucose injection demonstrates progressively declining beta cell function in autoantibody-positive relatives before the clinical onset of diabetes.[66]

Environmental Factors

Because only 30% to 50% of unaffected monozygotic identical twins of patients with type 1 diabetes melllitus will eventually develop the disease, it is likely that an environmental factor may be required to trigger the autoimmune destructive process.[67] A

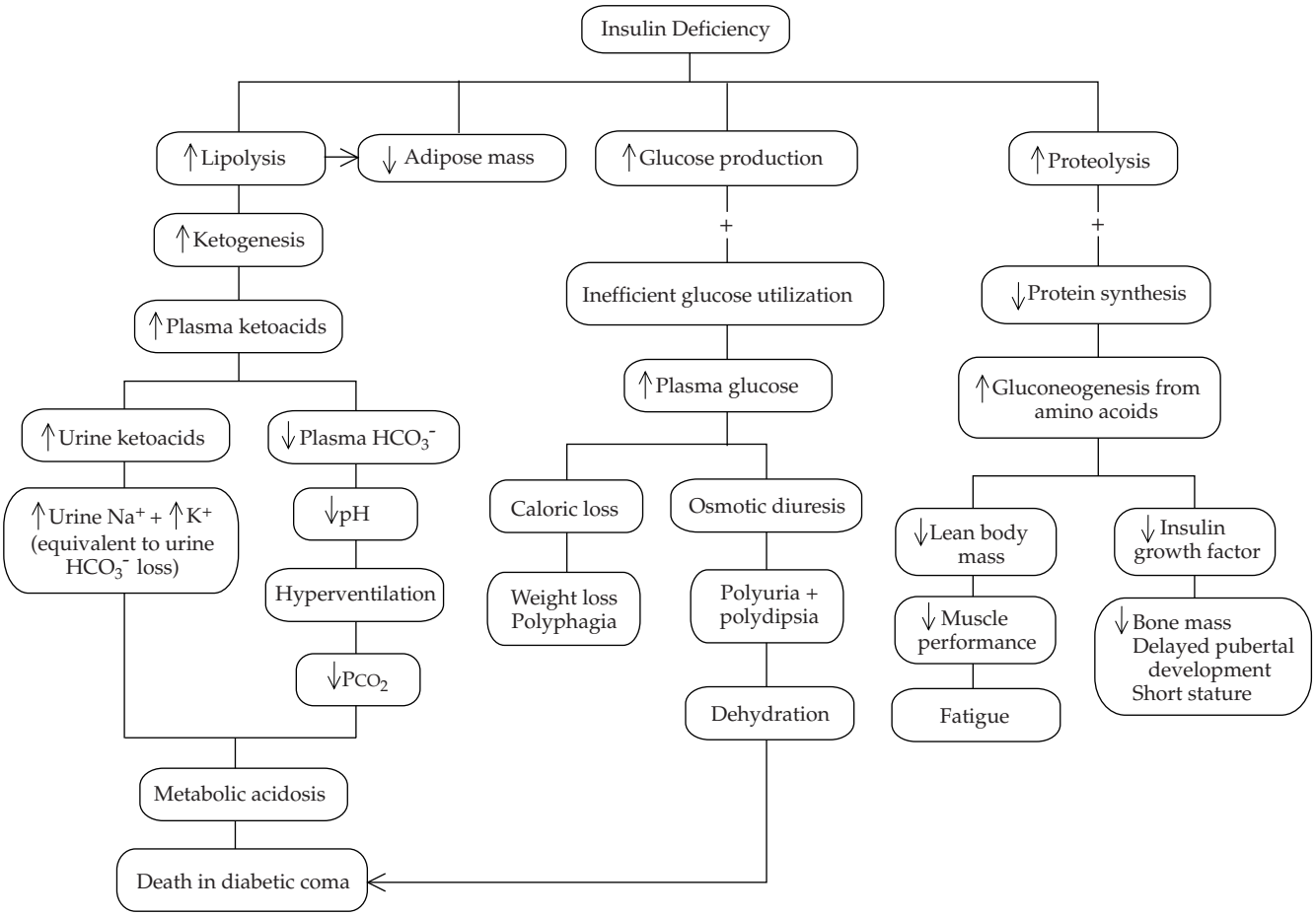

Figure 11 **Shown are the pathways that lead from insulin deficiency to the major clinical manifestations of type 1 diabetes mellitus. Note that a decrease in insulin growth factor also results from insulin deficiency and decreases growth rate.**

number of viral candidates have been proposed.[67] The only certain association is that offspring of women who are infected with rubella during pregnancy are at increased risk for type 1 diabetes mellitus. A small amount of indirect evidence also associates coxsackievirus B with type 1 diabetes mellitus.[68] Toxins in the environment or diet might also initiate the destruction of genetically vulnerable beta cells.

Temporal Sequence of Beta Cell Destruction

At the time of clinical onset of type 1 diabetes mellitus, at least a small number of beta cells are still potentially capable of function.[69,70] After several weeks of exogenous insulin treatment, particularly if exemplary metabolic control has been established,[71] dependency on exogenous insulin decreases or ceases entirely for weeks to months in some patients. This temporary so-called honeymoon remission phase is marked by an increase in serum C-peptide levels, which indicates an increase in endogenous insulin secretion [*see Figure 10*].[70] However, within 5 years after diagnosis of childhood type 1 diabetes mellitus, C-peptide virtually disappears from the serum.[72]

Type 1 diabetes mellitus does not develop in all autoantibody-positive individuals. Moreover, the latency period between initiation of beta cell destruction and appearance of the clinical disorder may be many years,[73] as the disease does not appear in some patients until considerably later in life. The gradual, indolent nature of the disease in these autoantibody-positive individuals is also suggested by the fact that some can be treated with beta cell–stimulating drugs before absolutely requiring insulin.[74] A trial sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases unfortunately found no evidence that type 1 diabetes mellitus can be prevented by inducing immune tolerance to exogenous human insulin given subcutaneously or orally to relatives of patients with high islet autoantibody titers.

Genetic Factors

Although a family history of type 1 diabetes mellitus is more likely to be absent than present in index cases, it is nonetheless true that offspring and siblings of patients with type 1 diabetes mellitus are at increased risk for the disease. There is a genetic basis for susceptibility to type 1 diabetes mellitus but not for inevitable development of the disease.[75] The disease will develop in 5% to 10% of first-degree relatives of patients with type 1 diabetes mellitus and in 20% of persons who have two first-degree relatives (e.g., both parents) with the disease. Association and linkage studies have incriminated a number of genes involved in the risk of type 1 diabetes mellitus. Polymorphism of HLA genes in the MHC locus on chromosome 6 account for 50% of the genetic risk.[75] DR3 and DR4 are susceptibility alleles that appear to operate synergistically. Individuals heterozygous for DR3 and DR4 are at greater risk than either homozygous DR3 or homozygous DR4 individuals. The DR2 allele decreases the risk and dominates the susceptibility effect of DR3 or DR4 when either is accompanied by DR2. The HLA-DQ locus also is associated with increased risk of diabetes.[76] Substitution of alanine, valine, or ser-

ine for the more usual aspartic acid at position 57 of DQ β chain or the presence of arginine at position 52 of DQ α chain increases the risk of type 1 diabetes mellitus. A number of mechanisms have been suggested to explain how HLA class II molecules might predispose to or protect against the disease.[77] Despite the accumulation of considerable knowledge, type 1 diabetes mellitus still cannot be predicted with complete certainty.[78]

Type 1 diabetes mellitus is associated with at least 15 additional loci on nine other chromosomes.[78] Of particular interest is that a variable number of tandem repeats in the promoter region of the insulin gene has been associated with the disease. However, the insulin molecule itself is apparently normal in structure in patients with type 1 diabetes mellitus. With the human genome soon to be fully known and advanced genetic technology becoming cost-effective, it is likely that the genetic components of type 1 diabetes mellitus will be sorted out in a way that will make it possible to identify susceptible individuals who might benefit from preventive therapies.

The clinical and biochemical manifestations of type 1 diabetes mellitus can all be accounted for as consequences of insulin deficiency [*see Figures 1 and 11*].[79] Loss of the stimulating effect of insulin on glucose uptake by muscle and adipose tissue coupled with loss of the suppressive effect of insulin on hepatic glucose output lead to severe hyperglycemia. FPG rises typically to 300 to 400 mg/dl, and postprandial glucose levels rise to 500 to 600 mg/dl in patients before treatment.[79] This increase presents a high filtered load of glucose to the renal tubules, causing a severe osmotic diuresis, manifested by polyuria and compensatory polydipsia. Loss of the lipogenic and antilipolytic effects of insulin on adipose tissue leads to high plasma levels and increased hepatic uptake of free fatty acids. This condition enhances ketogenesis, and ultimately, high plasma ketoacid levels cause metabolic acidosis. Protein breakdown is favored in the absence of the anticatabolic and anabolic actions of insulin. The proteolysis of muscle protein provides amino acids that sustain high rates of gluconeogenesis. Body-weight loss thus includes fat and lean body mass, and it is further aggravated by an increase in basal energy expenditure.[80] The negative nitrogen balance, accompanied by losses of potassium, magnesium, and phosphate in the urine, impairs growth and development in children.

DIAGNOSIS OF TYPE 1 DIABETES MELLITUS

The diagnosis of type 1 diabetes mellitus is still almost always made on the basis of symptom history confirmed by a blood or plasma glucose level greater than 200 mg/dl, with the presence of glucosuria and often ketonuria. The classic symptoms are polyuria, polydipsia, weight loss with normal or even increased food intake, fatigue, and blurred vision, commonly present 4 to 12 weeks before the symptoms are noticed. In the future, however, before clinical onset of type 1 diabetes mellitus, diagnosis may be possible with serologic methods, complemented by beta cell function tests.

MANAGEMENT OF TYPE 1 DIABETES MELLITUS

Of all chronic diseases, diabetes is unique because its therapy involves daily self-management by the patient and a host of lifestyle adaptations. For optimal metabolic control, patients must prick their fingers to test blood glucose at least four times daily, inject insulin at least three times daily, pay regular attention to the timing and content of their meals, and try to follow a scheduled exercise program. The patient is truly at the center of his or her care. Patient self-management requires intensive education with regard to the skills of injection and blood glucose monitoring, urine ketone testing on sick days, meal planning, detection and treatment of hypoglycemia, and management of intercurrent illness. Family members and close associates of the patient need to be included as is appropriate, particularly with regard to recognition and treatment of hypoglycemia. Ideally, the patient should understand the pathophysiology of diabetes and its long-term complications almost as well as health care professionals. Some aspects of care require periodic educational reinforcement, which is often stimulated by some therapeutic mishap, such as a preventable episode of severe hypoglycemia.

The clinical goals of treatment include (1) decreasing plasma glucose levels and urine glucose excretion to eliminate polyuria, polydipsia, polyphagia, caloric loss, and adverse effects such as blurred vision from lens swelling and susceptibility to infection, particularly vaginitis in women, (2) abolishing ketosis, (3) inducing positive nitrogen balance to restore lean body mass and physical capability and to maintain normal growth, development, and life functioning, (4) preventing or greatly minimizing the late complications of diabetes previously discussed. After publication of the DCCT results, The American Diabetes Association revised their standards of care accordingly [*see Table 3*] to include firm biochemical goals[81]: (1) maintaining preprandial capillary whole blood glucose levels at 80 to 120 mg/dl, bedtime blood glucose levels at 100 to 140 mg/dl, and postprandial peak blood glucose levels at less than 180 mg/dl, and (2) maintaining

Table 3 American Diabetes Association Standards* for Glycemic Control in Diabetes Mellitus[288]

Biochemical Index	*Normal*	*Goal*	*Additional Action Suggested*
Capillary whole blood values† (mg/dl)			
Average preprandial glucose level	< 110	80–120	< 80 > 140
Average bedtime glucose level	< 120	100–140	< 100 < 160
HbA_{1c} (%)	< 6	< 7	> 8

*The values shown in this table are by necessity generalized to the entire population of individuals with diabetes. Patients with comorbid diseases, the very young, older adults, and patients with unusual conditions or circumstances may warrant different treatment goals. These values are for nonpregnant adults. Additional action suggested depends on individual patient circumstances. Such actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacologic therapy, initiation of or increase in self-monitored blood glucose testing, or more frequent contact with the patient. HbA_{1c} is referenced to a nondiabetic range of 4.0% to 6.0% (mean, 5.0%; SD, 0.5%).
†To convert to plasma glucose values, add 10 mg/dl to whole blood values, except for 160 mg/dl, which becomes 180 mg/dl.

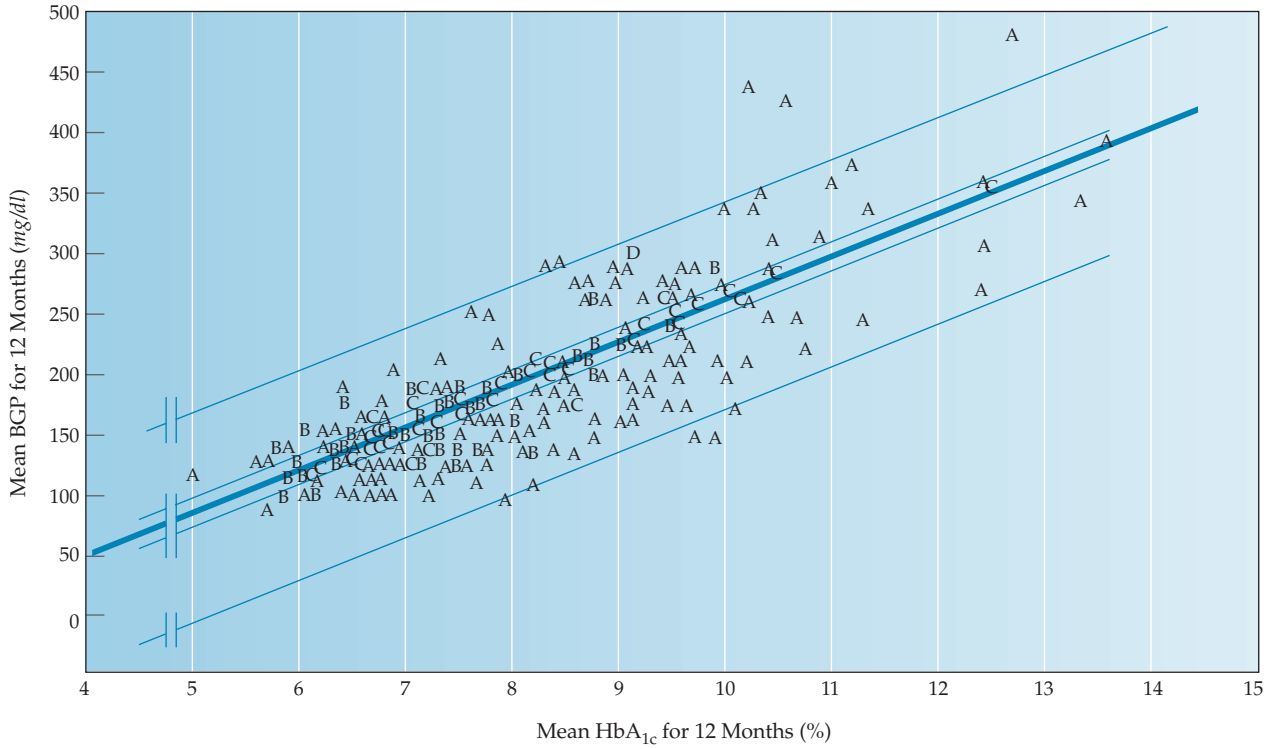

Figure 12 **The 12-month mean value of all seven-sample-a-day blood glucose profile values measured quarterly in the Diabetes Control and Complications Trial central biochemistry laboratory is plotted against the 12-month mean of quarterly HbA_{1c} values in the same patients. (A = 1 point, B = 2 points, C = 3 or more points; r = 0.80, $P < 0.001$)**

an HbA_{1c} of less than 7.0% (relative to a nondiabetic DCCT range of approximately 4.0% to 6.0%). Realistically, current therapeutic tools make it difficult to achieve these stringent goals in many patients with type 1 diabetes mellitus, particularly those with absolutely no endogenous insulin secretion. The exponential relation between the risk of microvascular complications and HbA_{1c} predicts that only normal HbA_{1c} levels would completely prevent the complications. However, maintaining an HbA_{1c} below 7.0% will remove much of the absolute risk from most patients. Efforts to achieve an HbA_{1c} of less than 7.0% should continue as long as hypoglycemia can be minimized.

Monitoring of Glycemic Control

In the past 5 to 10 years, blood glucose meters have undergone continuous development and improvement. They are now smaller, use less blood and more sites for puncture, are less vulnerable to inaccuracy because of patient errors, and have memory programs that allow the patient or caregiver to assess the pattern of blood glucose control over the previous 2 months, largely eliminating the problem of incorrect or fabricated written transcription of results. Devices that can accurately estimate blood glucose without a blood sample have been in development for a number of years but have not reached a state of reliability suitable for clinical practice. An indwelling subcutaneous catheter for blood glucose monitoring that can be used for 3 days and provide frequent readings is now available. Although the recorded profile can provide only a brief window into a lifetime of blood glucose fluctuation, such a profile can guide periodic adjustments of the regimen.

Currently, even with its imperfections, blood glucose testing before each meal or large snack is essential if the patient is to adjust each dose of rapid-acting insulin to the level of blood glucose before the meal and to the amount of carbohydrate about to be ingested. Blood glucose levels also need to be periodically checked after meals to ensure that undue postprandial hyperglycemia is not occurring. Patients should also check blood glucose levels before or after intensive exercise to prevent or abort hypoglycemia. It is very important to check blood glucose levels before driving to prevent motor vehicle accidents brought on by severe hypoglycemia, which can have adverse effects on drivers' judgment and reaction times. Occasional 3:00 A.M. blood glucose readings are useful in monitoring for otherwise unrecognized frequent nocturnal hypoglycemia. Most important, during intercurrent illnesses, especially those accompanied by nausea, vomiting, and limitation of fluid and caloric intake, patients must test blood frequently to guide insulin treatment. In addition, under these circumstances, the risk of ketoacidosis mandates testing of urine or blood for ketoacids. The presence of significant levels of ketoacids is a signal to call the caregiver immediately and establish frequent contact for instructions regarding insulin doses and carbohydrate intake.

A critical supplement to home blood glucose testing is monitoring of HbA_{1c} in the physician's office. It is now well established that this product of nonenzymatic glycation provides an excellent index of average blood glucose levels [*see Figure 12*] for approximately the preceding 2 months.[82,83] In at least one study, patients whose HbA_{1c} was measured periodically had a better health status, lower glycemic levels, and fewer hospitalizations than a randomly selected group of patients whose HbA_{1c} level remained unknown to both the patient and the physician.[84] Quarterly HbA_{1c} measurements are satisfactory except during pregnancy, when monthly levels should be obtained. Because methods and results vary among laboratories, a national glycohemoglobin standardization program is under way, and HbA_{1c} should be measured in laboratories certified to provide DCCT-equivalent results.[85] Use of rapid-turnaround, point-of-service

HbA_{1c} assays improves the efficiency with which diabetes caregivers can modify patients' regimens on office visits and improves treatment results.[86] Assays of other products of nonenzymatic glycation, such as fructosamine and glycated albumin, that reflect shorter periods of chronic glycemia are less useful in routine diabetes management.[85]

Insulin Types and Delivery

Correction of insulin deficiency is the most critical component in managing type 1 diabetes mellitus. Before the availability of insulin, patients with type 1 diabetes mellitus and complete insulin deficiency inevitably followed a predictable downhill course [*see Figure 11*] and died either in diabetic coma or essentially of starvation and inanition. Insulin extracted from beef and pork pancreas and purified to increasingly high levels was the mainstay of therapy until recombinant DNA technology made it possible to produce authentic human insulin in large quantities. Although animal insulins are therapeutically bioequivalent to human insulin, they disappeared from the market as manufacturers switched over to making only human insulin. In rare instances of local allergy to human insulin, lispro insulin (see below) can be substituted. In emergency situations, patients with systemic allergy to human insulin can be desensitized by administering extremely small amounts and gradually increasing the dose over 6 to 24 hours until the patient is tolerant and responsive to human insulin.

The basic principle of insulin replacement[87,88] is to provide a slow, long acting, continuous supply that mimics the nighttime and interprandial basal secretion by normal beta cells. In addition, a rapid and relatively short-acting form of insulin delivered before meals mimics the normal meal-stimulated burst of insulin secretion [*see Figure 2*]. A number of insulin preparations for subcutaneous administration are currently available [*see Table 4*]. It is important to recognize that there is considerable variability in the pharmacokinetic characteristics of these insulins both from individual to individual and within the same individual from day to day. Rates of insulin absorption from the skin vary with the injection site, the depth and angle of injection, ambient temperature, and exercise of an injected limb. Injection into the subcutaneous tissue of the abdomen produces the least variable results. The expected therapeutic action can also be affected by fluctuations in sensitivity to insulin from time to time in patients. Despite the variability of results, certain average patterns can be expected from the multiple daily injection regimens in common use [*see Figure 13*]. CSII by use of an external pump provides smooth basal delivery and somewhat more predictable acute increases in plasma insulin for meals. Only crystalline zinc insulin (regular insulin) and lispro insulin are used in such pumps, which is one reason for their greater consistency of effect.

Synthetic Insulin Analogues

Lispro was the first of what undoubtedly will be many new insulin analogues with structures designed to provide pharmacokinetics that more closely mimic physiologic insulin secretion and needs.[89] One of the features of natural (or synthetic) human insulin is that six molecules associate with a zinc molecule to form hexamers. Insulin hexamers must disassociate to monomers before they can be absorbed from subcutaneous injection sites. This requirement is the main reason that crystalline zinc insulin (regular insulin) has a peak action 2 to 4 hours after injection and must be taken 30 to 60 minutes before eating to have any chance of limiting postprandial hyperglycemia. By simply exchanging lysine and proline at positions 28 and 29 of the B chain of insulin [*see Figure 3*], hexamer formation is prevented and the monomer is rapidly absorbed from an injection site. Lispro insulin action begins within 15 minutes, the peak effect is reached at 1 to 2 hours, and the duration of action is only 4 to 6 hours. Thus, lispro insulin injected just before a meal provides a postprandial plasma insulin profile similar to that of normal human insulin secretion [*see Figure 2*]. The chief benefits of using lispro insulin are to reduce postprandial blood glucose peaks and to somewhat decrease the hypoglycemia that can result from the late tail of regular insulin action.[90,91] However, loss of that late action can lead to recurrent hyperglycemia before the next meal. Hence patients switched from regular insulin to lispro insulin may have no reduction in HbA_{1c} unless their doses of basal insulin (neutral protamine Hagedorn [NPH], Lente, or Ultralente or the basal rate in CSII) are increased.[92] It may even prove useful to combine lispro insulin with regular insulin in a single injection to optimize postprandial control.

Another synthetic rapid-acting analogue, insulin aspart, replaces proline with aspartic acid at position B28 [*see Figure 3*]. This substitution leads to a profile of action and therapeutic benefits that are very similar to those of lispro insulin.[93] A long-acting analogue, glargine, has also been synthesized as a basal insulin with no discernible peak and a longer duration of action than Ultralente insulin.[94,95] Glargine has two additional arginines at the carboxyl terminus of the B chain, B31 and 32, and has a glycine for arginine substitution at position A21 [*see Figure 3*]. Glargine is giv-

Table 4 Insulin Preparations

Insulin Type	*Onset (hr)*	*Duration (hr)*	*Peak (hr)*
Rapid acting (regular, crystalline zinc insulin [CZI])	0.5–1.0	6–8	2–3
Very rapid acting			
Lispro	0.25–0.5	4–6	1–2
Insulin aspart	0.25–0.5	4–6	1–2
Intermediate acting			
Lente, neutral protamine Hagedorn (NPH)	1	10–14	4–8
Long acting			
Ultralente	1	18–24	Minimal at 10–14
Glargine	1.5	30	None

en as a single bedtime injection to provide basal insulin for 24 hours with less nocturnal hypoglycemia.[96] For reasons that should now be clear, intensive treatment regimens are the preferred form of therapy and should be implemented early in as many patients as is safely possible. Different combinations of insulin preparations can be used to approximate (but never reliably reproduce) normal plasma insulin profiles [*see Figure 13*]. Type 1 diabetes mellitus can almost never be satisfactorily controlled on less than two injections a day of intermediate- or long-acting insulin combined with rapid-acting insulin. Only in patients experiencing a honeymoon remission or in patients with late-onset autoimmune type 1 diabetes mellitus in adults can satisfactory metabolic control be established with a single injection of insulin daily. Such success is made possible only by the presence of some normally regulated endogenous insulin secretion.

Insulin Regimens

As a rule of thumb, basal insulin and mealtime insulin pulses each constitute approximately 50% of the average total daily dose (0.6 to 0.7 U/kg) in intensive-therapy regimens. The dose of regular or lispro insulin or insulin aspart before each meal is chosen by the patient on the basis of the blood glucose level, the estimated amount of carbohydrate to be eaten, or both. A typical regimen would call for 1 to 2 extra units of insulin for each 50 mg/dl increment in blood glucose above the dose called for by the preprandial target of 80 to 120 mg/dl, or 1 U/10 to 15 g of extra carbohydrate to be ingested above the usual amount of carbohydrate prescribed by the nutrition plan. Very sophisticated patients can combine both guidelines. Glargine is rapidly achieving dominance as the basal insulin.

Fixed-dose mixtures of insulin are not physiologically very suitable for patients with type 1 diabetes mellitus. However, for patients who can or will implement only such conventional treatment, a typical regimen might be a total daily dose of 0.6 to 0.7 U/kg. Two thirds to three fourths of the dose would be given before breakfast and the remainder before supper; the ratio of intermediate-acting insulin to rapid-acting insulin might be 2:1 to 4:1 before breakfast and 1:1 before supper. Because giving NPH or Lente insulin before supper increases the risk of hypoglycemia between 2:00 and 4:00 A.M., patients on conventional treatment should be urged to switch to a three-injection regimen, taking the evening dose of intermediate-acting insulin at bedtime to avoid nocturnal hypoglycemia and to better control the prebreakfast blood glucose level. Glargine insulin may also be helpful in minimizing nocturnal hypoglycemia.[87,88]

Insulin requirements are increased by greater caloric and especially carbohydrate intake, by weight gain of both lean body mass and fat mass, by the onset of puberty, by infections and other medical or surgical stresses, by pregnancy, by glucocorticoid administration, and sometimes by the physiologic changes that pre-

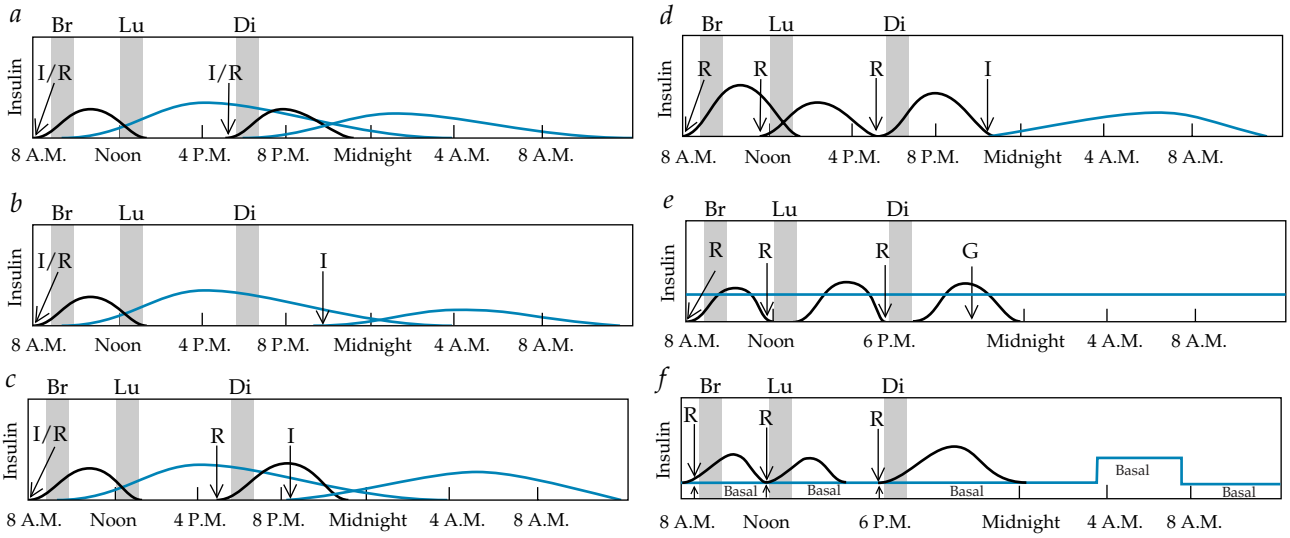

Figure 13 **Different combinations of various insulin preparations can be employed in establishing glycemic control in type 1 diabetes mellitus (and in those patients with type 2 diabetes mellitus who eventually reach an equivalent degree of insulin deficiency). Arrows indicate time of injection. Red curves represent rapid-acting (R) regular or lispro insulin. Blue curves represent intermediate-acting (I) NPH or Lente insulin. Gray curves represent long-acting insulin glargine (G). (*a*) A mixed injection of I and R insulin is administered before breakfast and dinner in this average regimen. In addition to the risk of hypoglycemia before lunch and in the late afternoon, the predinner administration of I insulin predisposes patients to hypoglycemia from 2:00 A.M. to 4:00 A.M. (*b*) This average regimen combines a mixed injection of I and R insulin given before breakfast with an injection of I insulin given before bed. The I insulin administered at bedtime provides safer, more effective overnight glucose control; without predinner insulin, however, glucose levels may rise to unacceptably high levels after dinner. (*c*) In this intensive regimen, the patient receives three injections: a mixed injection before breakfast, R insulin before dinner, and I insulin before bed. (*d*) This intensive regimen combines three preprandial injections of R insulin with one injection of I insulin before bed. Preprandial doses of R insulin are adjusted according to glucose levels and meal size. (*e*) This intensive regimen uses long-acting insulin glargine to replace basal insulin secretion. Preprandial doses of R insulin are adjusted according to blood glucose levels and anticipated meal carbohydrate content. (*f*) This intensive regimen provides only R insulin as regular or lispro insulin. A pump-driven continuous subcutaneous infusion of R insulin replaces basal insulin secretion. Basal rates can vary during different times of day or activities. For example, the basal rate can be lowered or even suspended during periods of intensive aerobic exercise. The nocturnal basal rate can be increased 1.5 to 2.0 times from 3:00 A.M. to 4:00 A.M. until breakfast to accommodate the rising early morning insulin requirement known as the dawn phenomenon. Preprandial bolus doses are individually dialed in and rapidly pumped in, adjusted according to blood glucose levels and anticipated meal carbohydrate content. (Br = breakfast, Lu = lunch, Di = dinner)**

cede the onset of menses. During acute illnesses, patients will require extra doses of rapid-acting insulin when hyperglycemia accelerates and especially if ketosis occurs. Frequent telephone contact with caregivers allows timely professional guidance of the extra insulin doses, nutrient intake to prevent hypoglycemia, and fluid intake to prevent dehydration. Lispro insulin or insulin aspart is especially useful in these circumstances because the effect of an overdose is short lived and hypoglycemia is less likely.

CSII has improved considerably since its introduction in the 1970s.[97] Modern insulin infusion pumps permit programming with multiple basal rates, allowing flexibility during the day as well as automatic adjustment of doses while sleeping at night. Frequently, the basal rate needs to be lower in the first half of the night and then increased to accommodate the so-called dawn phenomenon [*see Figure 13*]. The latter is a slow rise in the plasma glucose level before the patient awakens, demonstrable in normal individuals but exaggerated in individuals with type 1 diabetes mellitus who cannot limit it by increasing endogenous insulin secretion. On the other hand, interruption of insulin delivery from a pump for as little as 8 hours can result in extreme hyperglycemia, diabetic ketoacidosis (DKA), and hyperkalemia. In the DCCT, patients who used an insulin pump had a slightly but significantly higher DKA event rate (1.8 per 100 patient-years) than patients on multiple daily injection regimens (0.8 per 100 patient-years).[98] There was no difference in risk of severe hypoglycemia between patients treated with insulin pumps and patients treated with multiple daily injections, although episodes resulting in coma or seizure were more common in CSII-treated patients.[98] The rate of infection at catheter sites was kept very low by frequent change of catheters and preemptive use of antibiotics at the first visible signs of infection. Pump use has grown exponentially in the past 10 years; 200,000 patients now use pumps.

Avant-garde Therapy

Implantable pumps delivering insulin into the peritoneal cavity and resulting in a more physiologic first pass of insulin through the liver have provided acceptable HbA_{1c} levels with a lower frequency of severe hypoglycemia.[99] Difficulties with obstruction of insulin delivery and infection have occurred, and they are not yet approved for commercial use. Closed-loop insulin-delivery devices that would measure the patient's blood glucose level very frequently and would automatically adjust insulin delivery still await the development of a practical and long-lived indwelling continuous glucose sensor.

Insulin can be absorbed through the mucosa of the nose and also through the lungs. A nasal preparation of insulin has been effective in short-term clinical trials, but the disadvantages of high cost (10 times the subcutaneous insulin dose is needed to achieve the same blood glucose lowering) and failure to develop a vehicle that does not cause allergic nasal symptoms have prevented this preparation from being used in practice.[100] Inhaled insulin, with various delivery devices, is still undergoing clinical trials.[101,102] The pharmacokinetic properties of inhaled insulin resemble those of lispro insulin and insulin aspart, so inhaled insulin is suitable for preprandial use. Various attempts to package insulin for oral administration so as to prevent its degradation in the gastrointestinal tract have also been investigated, as has transdermal insulin.

Pancreas transplantation remains controversial as a routine form of insulin replacement therapy.[103] Over the period of 1994 to 1997, 1-year graft survival rates were 82% when a pancreas was transplanted with a needed kidney transplant and 62% when a pancreas was transplanted alone.[104] Successful pancreas transplants provide nondiabetic HbA_{1c} levels and free the patient from the rigors of diet, blood glucose testing, and insulin injection, and they virtually eliminate episodes of hypoglycemia.[104] Quality of life is usually improved. On the negative side, the patient incurs the risk of operative mortality and morbidity and must remain on immunosuppressive therapy with its attendant risks of infection and malignant disease.[103] Length of stay, readmission rates, morbidity, and the number of acute rejection episodes are higher for pancreas transplants than for kidney transplants. From 1994 to 1996, the 1-year pancreas transplant survival was 81%, compared with a kidney transplant survival of 88%.[103] The large majority of pancreas transplantations are still performed as an option in conjunction with a necessary kidney transplant.

Transplantation of isolated islets can be accomplished without major surgery. Furthermore, the ability to immunomodulate isolated islets in the laboratory (by masking or removing cell surface antigens) may someday allow transplantation with little or no immunosuppression. Alternatively, islets can be placed in semipermeable hollow tubes that allow glucose to enter and insulin to leave but shield the islets from inflammatory reactions to a foreign body. Islet transplantation with function lasting at least 1 year has been achieved in less than 10% of attempts worldwide. A Canadian group has reported on seven successive cases of islet injection into the liver, with persistent function and independence from insulin injections for up to 15 months, using a new immunosuppressive regimen.[105] This technique is undergoing a multicenter trial.

Nutritional Therapy and Exercise

Intensive and conventional insulin treatment will produce unsatisfactory results unless it is appropriate for the nutrient intake. To facilitate the matching of insulin doses to meals and to prevent hypoglycemia, patients with type 1 diabetes mellitus should eat consistent regular meals comprising about 50% carbohydrate calories, less than 30% total fat calories, and less than 300 mg cholesterol a day.[106] Various methods of teaching patients how to assess amounts of foods and their nutrient and caloric content have been utilized. These methods include exchange lists that place foods into six categories; each category has approximately the same quantity of carbohydrate, protein, and calories per serving. These exchange categories are bread, meat, milk, fruit, fat, and vegetable. Another approach is to focus only on the carbohydrate content of foods because carbohydrates cause most of the postprandial hyperglycemia. Because different carbohydrates are digested and absorbed at different rates and therefore have different effects on plasma glucose levels, glycemic indices have been developed for common foods that help adjust for their different effects.[107] It is noteworthy that numerous studies have disproved the myth that sucrose raises blood glucose more than equivalent amounts of other carbohydrates.[108] For optimal instruction and reinforcement of diet therapy, a dietitian should be part of the diabetes care team.

Exercise is another important component of diabetes care because it helps maintain cardiovascular conditioning, insulin sensitivity, and general well-being.[109] However, patients must be instructed how to adjust their meals, their insulin doses and timing, or both to prevent hypoglycemia during, immediately after, or even 6 to 12 hours after exercise as muscle glycogen stores are replenished from plasma glucose. High-impact sports are contraindicated for patients with advanced retinopathy who are at risk for vitreous hemorrhage or for patients with peripheral neuropathy or vascular disease who are at risk for foot trauma, because such sports can be hazardous.

Table 5 Typical Laboratory Findings and Monitoring in Diabetic Ketoacidosis

Test	*Average*	*Range*
Plasma glucose	600 mg/dl (33 mmol/L)	200–2,000 mg/dl (11– 110 mmol/L)
Plasma ketones (positive)	1:16	1:2–1:64
Blood betahydroxybutyrate (mmol/L)	—	3–25
Plasma HCO_3 (mEq/L)	10	4–15
Blood pH	7.15	6.80–7.30
Pco_2 (mm Hg)	20	14–30
Plasma anion gap (Na^+ – [CI + HCO_3]) (mEq/L)	23	16–30

Perform complete blood count, serum urea nitrogen measurement, serum creatinine measurement, urinalysis, appropriate cultures, and chest radiography.

1. Weigh on admission and every 12 hr.
2. Record cumulatively intake and output every 1 to 2 hr (Foley catheter if incontinent).
3. Check blood pressure, pulse, respiration, mental status every 1 to 2 hr and temperature every 8 hr.
4. Check blood (fingerstick) or plasma (laboratory) glucose every 1 to 2 hr.
5. Check serum potassium every 2 to 4 hr; check other electrolytes and serum ketones or betahydroxybutyrate every 4 hr.
6. Check arterial blood pH and gases on admission (in children, venous pH may be substituted; add 0.1 to result). If pH < 7.0 on admission, recheck as required until pH exceeds 7.1.
7. Check serum phosphate, magnesium, and calcium levels on admission. If low, repeat every 4 hr; otherwise, every 8 to 12 hr.
8. Spot-check voidings for ketones and glucose.
9. Perform ECG on admission; repeat if follow-up serum potassium level is abnormal or unavailable.

Note: 1–9 should be carried out until the patient is stable, glucose levels have reached and are maintained at 250 mg/dl, and acidosis is largely reversed (plasma HCO_3 > 15–18, plasma anion gap < 16). An intensive care setting is preferred.

DIABETIC EMERGENCIES IN TYPE 1 DIABETES MELLITUS

Diabetic Ketoacidosis

DKA is the ultimate result of insulin deficiency[110,111] [*see Figure 11*], which is aggravated by stress-induced elevations of glucagon, cortisol, growth hormone, epinephrine, and norepinephrine[110] that add a component of insulin resistance.[112] DKA occurs in 2% to 5% of patients with type 1 diabetes mellitus a year. In the closely followed DCCT patients, overall event rates were 2.0 per 100 patient-years in the intensively treated group and 1.8 per 100 patients-years in the conventionally treated group.[34] Reported mortality varies worldwide from as low as 0% to as high as 10%. Most cases occur in patients already diagnosed with type 1 diabetes mellitus, but DKA still can be the first manifestation of diabetes, especially in children. Self-monitoring of blood glucose and urine ketones and close contact with the diabetes care team should facilitate recognition and abortion of evolving DKA by early and aggressive treatment with extra insulin and fluids at home. Approximately half the cases of DKA are precipitated by infection. Sepsis, myocardial infarction, and other major intercurrent illnesses are more often the cause of death than the metabolic disequilibrium itself. In children, cerebral edema rarely occurs. It usually appears 6 to 12 hours after treatment is initiated when biochemical improvement is manifest; yet it is often fatal.

Presenting features DKA presents with signs and symptoms of dehydration secondary to osmotic diuresis and vomiting and, sometimes, to diarrhea caused by concurrent gastroenteritis; of compensatory hyperventilation to eliminate CO_2; and of various degrees of depressed mentation or decreased consciousness. Seizures are notably not a result of DKA. Complete coma almost certainly indicates a long period of DKA before medical attention. DKA yields a number of characteristic laboratory findings [*see Table 5*]. The anion gap metabolic acidosis is secondary to elevated levels of acetoacetate and betahydroxybutyrate with small contributions from lactate and free fatty acids. Although serum potassium and phosphate levels are usually normal or even high initially, this finding masks a profound total body depletion of these electrolytes, along with magnesium. Deviations from the customary pattern create pitfalls in diagnosis. Ketones, which current tests detect only as acetoacetate or acetone, may be missing from the serum if the redox potential of the patient is very high and the equilibrium of the ketoacids is shifted toward the reduced partner betahydroxybutyrate (as may occur in alcohol intoxication). Serum bicarbonate levels may be normal if there is coexisting respiratory acidosis. Arterial blood pH may be normal if there is coexistent metabolic alkalosis caused by diuretic ingestion or pernicious vomiting. Occasionally, plasma glucose levels are less than 250 mg/dl because of fasting,[113] high alcohol intake, profound inanition, or pregnancy.

Treatment Treatment of DKA[110,114,115] requires careful monitoring of the patient [*see Table 5*]. Volume repletion is as important as insulin therapy.[116] Intravenous 0.9% saline should be started even before the diagnosis is established. After an initial liter in 30 to 60 minutes, fluid therapy should continue aggressively until the circulating volume is replenished, as indicated by an increase in blood pressure to normal and a reduction in compensatory tachycardia. Subsequent total volume repletion is carried out more slowly at 150 to 500 ml/hr with 0.45% saline, switching to 5% glucose-containing solutions once plasma glucose has decreased to 250 mg/dl. Typical fluid deficits range from 50 to 100 mEq/kg. Average sodium deficits are 7 mEq/kg, and most important, potassium deficits may be as high as 7 mEq/kg. The effective depletion of total body bicarbonate through loss of the strong organic acids acetoacetate and betahydroxybutyrate in the urine is revealed later, when a hyperchloremic metabolic acidosis often ensues. Potassium repletion (10 to 40 mEq/hr) should begin promptly after insulin administration and as soon as hyperkalemia and oliguria or anuria have been ruled out [*see Table 5*]. Otherwise, serious hypokalemia will result as insulin stimulates potassium uptake by cells [*see Figure 4*]. If the serum potassium level is less than 40 mEq/L on admission, a very large deficit exists and repletion should be at a faster rate to maintain a level no lower than 3.5 to 4.0 mEq/L. Insulin should be withheld in such circumstances until serum potassium reaches 4.0 mEq/L. Hypokalemia is the most tragic cause of death resulting from therapeutic misjudgment.

Although DKA can be managed satisfactorily with insulin given intramuscularly or subcutaneously, intravenous administration is far more reliable and results in fewer instances of hypokalemia and hypoglycemia. A bolus of 10 U or 0.1 U/kg is followed by the same dose given hourly by intravenous infusion, preferably with a pump and through its own intravenous line. Routine addition of sodium bicarbonate or potassium phosphate has not been found to hasten recovery in ordinary cases of DKA.[115] Possible indications for administration of sodium bicarbonate (50 to 200 mEq)

include arterial pH less than 7.0, ECG changes of hyperkalemia, hypotension that does not respond to rapid infusion of 0.9% saline, and left ventricular failure. If bicarbonate therapy is given, serum potassium and arterial pH should be monitored hourly and extra potassium given to prevent hypokalemia. Rhabdomyolysis, hemolysis, and central nervous system deterioration can be caused by severe hypophosphatemia (<1.5 mg/dl) and call for intravenous administration of 60 mmol (approximately 2 g) of phosphate as the potassium salt over 6 hours. Once the anion gap has decreased to near normal and bicarbonate has risen to 15 to 18 mEq/L, the insulin infusion rate can be decreased to 2 U/hr. In general, it is best to maintain the insulin infusion at 1 to 2 U/hr with accompanying 5% glucose infusion, aimed at keeping the plasma glucose level at around 150 mg/dl until the following morning, when a subcutaneously mixed insulin regimen can be started or resumed along with a diet.

It is preferable to treat patients with DKA in an intensive care unit to ensure close monitoring. Persistent vomiting calls for gastric intubation, and the airway of an obtunded patient should be protected to prevent aspiration. Any suspicion of sepsis mandates treatment with broad-spectrum antibiotics.

Hypoglycemia

Hypoglycemia is a more common emergency than DKA and potentially as dangerous. Clinical hypoglycemia can range from annoying symptoms accompanying a biochemically low blood glucose level (< 50 to 60 mg/dl) to confusion, seizures, or coma. Any episode that requires intervention by another person to reverse is categorized as severe hypoglycemia. Severe hypoglycemia can have disastrous consequences, particularly if the patient is driving any sort of vehicle, working at heights, or operating potentially dangerous machinery.

The most common causes of hypoglycemia are missed meals and snacks,[117] insulin dosage errors, exercise, alcohol, and drugs such as beta-adrenergic blockers. During the DCCT, 55% of hypoglycemic episodes occurred during sleep.[117] Such episodes often go undetected.[118]

Glucagon and epinephrine are the major counterregulatory hormones that are secreted in response to hypoglycemia.[119] Both restore glucose levels by increasing hepatic glucose output, while epinephrine also decreases the sensitivity of muscles to insulin. Furthermore, catecholamine secretion alerts the patient to treat the episode because it produces the sympathoadrenal symptoms noted below. Cortisol and growth hormone are also secreted in response to hypoglycemia[119] and play a role in maintaining glucose levels but not in rapid recovery from hypoglycemia.

Presenting features The most common symptoms of early mild hypoglycemia are adrenergic and include tachycardia, tremulousness, anxiety, and sweating.[120] The last symptom requires sympathetic activation of cholinergic nerves innervating the sweat glands.

Factors affecting severity of hypoglycemic episodes The development of primary or secondary adrenal insufficiency, hypopituitarism, and hypothyroidism may increase the risk of hypoglycemia by increasing sensitivity to insulin, decreasing appetite, or both. Stress, exercise, or use of alcohol or illicit drugs may blunt or prevent recognition of hypoglycemia. Patients who do recognize incipient hypoglycemia but who consciously do not respond expeditiously (for example, they may wait for a meal in a restaurant or continue to drive after symptoms first appear) are also at increased risk for severe hypoglycemia. Moreover, some risk factors for hypoglycemia have multiple effects that can precipitate, prolong, or worsen the severity of hypoglycemia. Alcohol, for instance, impairs judgment and inhibits gluconeogenesis and hepatic glucose output, thereby delaying recovery. When hypoglycemia is inadequately treated, more severe hypoglycemia often ensues.

Finally, because glucagon and epinephrine are the major defense hormones against prolonged hypoglycemia, their absence promotes longer and more severe episodes by two mechanisms: (1) compensatory hepatic glucose output is decreased when not stimulated by glucagon or epinephrine and (2) the familiar adrenergic symptoms may cease in the absence of epinephrine, resulting in failure to recognize the episode.[119] The glucagon response to hypoglycemia often wanes in patients after they have had type 1 diabetes mellitus for a few years. In the absence of glucagon, epinephrine secretion still provides adequate counterregulatory defense; however, epinephrine response can also be lost eventually, sometimes in association with other autonomic neuropathies and sometimes selectively. Many patients lose the ability to counterregulate against hypoglycemia during the first 10 years that they have type 1 diabetes mellitus.

Given the importance of intensive regimens to prevent microvascular complications from hyperglycemia, it is most unfortunate that a lowered glucose threshold for release of glucagon and epinephrine in response to hypoglycemia has been observed, particularly in patients undergoing intensive insulin therapy.[121] The lowered glucose level needed to stimulate counterregulation narrows the safety margin of therapy. For instance, the first symptom of hypoglycemia may occur only at glucose levels as low as 35 mg/dl (as opposed to 55 to 60 mg/dl) and may consist of confusion or loss of judgment, which interferes with self-treatment. Some evidence suggests that unawareness of hypoglycemia is self-generating, because each episode may lower the threshold at which autonomic counterregulation begins in subsequent episodes.[119] The converse of this is that a period free of hypoglycemia, produced by daily therapeutic contact with caregivers, may restore hypoglycemia awareness,[122,123] though it may not restore normal counterregulatory responses.[122] Increased uptake of glucose by the brain in the presence of hypoglycemia[124,125] is a likely explanation for the relative infrequency of clinical hypoglycemic catastrophes.

Treatment Patients recognize most episodes of hypoglycemia quickly and can effectively treat themselves with a promptly absorbed oral carbohydrate. Approximately 15 g of carbohydrate is sufficient to restore blood glucose levels to normal. This amount is provided by approximately 6 oz of orange juice, 4 oz of a cola drink, 3 to 4 tsp of table sugar, five Life Savers, or three glucose tablets (each containing 5 g of glucose). The use of complex carbohydrates and foods with a high fat content, such as chocolate, may delay digestion and absorption of the glucose and are not first choices for treatment of hypoglycemia. If the patient cannot swallow or cooperate, a gel form of glucose and simple carbohydrates can be administered by mouth, applying it between the gums and cheeks, from where it slowly and generally safely trickles down into the stomach. Glucagon (1 mg administered subcutaneously or intramuscularly) will also usually raise blood glucose levels sufficiently within 15 to 30 minutes, when the patient can then take oral carbohydrates. Glucagon comes in emergency kits, and it should always be on hand for patients with a history of severe hypoglycemic episodes. Glucagon may

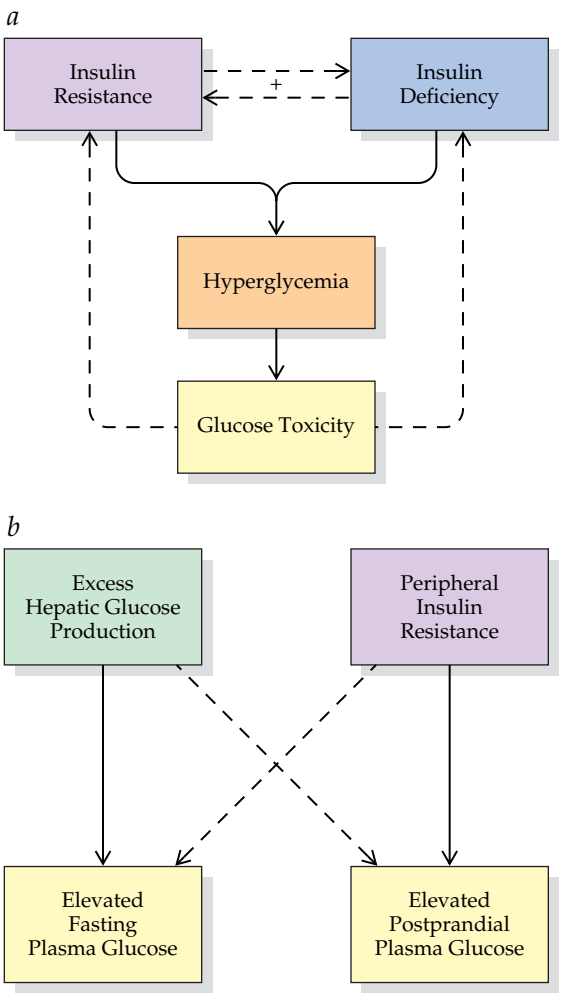

Figure 14 **(*a*) The interrelations of insulin resistance, insulin deficiency, and glucose toxicity that create overall hyperglycemia in type 2 diabetes mellitus are depicted. Insulin resistance and insulin deficiency are mutually reinforcing factors. Glucose toxicity refers to the secondary aggravating effects of hyperglycemia that both increase insulin resistance and reduce beta cell function. The glucose toxicity is diminished or eliminated by any therapy that lowers blood glucose. (*b*) Once fasting glucose levels are abnormal, they are correlated with and largely driven by the excess hepatic glucose production. Abnormal postprandial glucose levels are largely a consequence of peripheral insulin resistance that makes glucose utilization in muscle and adipose tissue inefficient. Insulin deficiency plays an increasingly important role in elevating both fasting and postprandial glucose levels as time goes on.**

cause nausea, vomiting, and headache, especially in children. When all else fails, intravenous glucose must be given by emergency medical service personnel or in an emergency room, whichever is quicker. When the timing of an episode suggests it was caused by intermediate- or long-acting insulin or by prior exercise, blood glucose may fall to hypoglycemic levels again and re-treatment may be necessary. Thus, a patient who has required assistance from others in reversing hypoglycemia should be kept under surveillance for some time thereafter.

Patients with severe hypoglycemia usually respond rapidly to treatment, although patients who are postictal or in a prolonged coma may require days to regain normal mental status and cognitive function. Quite often, there is amnesia for such extended episodes, including a period preceding the onset of hypoglycemia. In rare instances, neurologic deficits can be permanent. In general, however, long-term consequences of hypoglycemia have not been detected in adults.[126,127] In view of the potential consequences of prolonged episodes, hypoglycemia should always be treated immediately.

Prevention Patients should be instructed to treat themselves as though they have hypoglycemia whenever they suspect it, even if they are unable to do a confirmatory blood glucose test at the time. The threshold for symptoms of hypoglycemia varies from person to person and even varies in the same person on different occasions. Therefore, whenever possible, a confirmatory blood glucose test should be done to help the patient discriminate nonspecific symptoms from true hypoglycemia. Patients at increased risk for severe hypoglycemia should monitor their blood glucose levels more frequently.

Type 2 Diabetes Mellitus

PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

Insulin Resistance and Insulin Deficiency

The pathogenesis of type 2 diabetes mellitus[128] is even more complex than that of type 1 diabetes mellitus. Insulin resistance, reported in 92% of one large group of people with type 2 diabetes mellitus,[129] plays a major role in generating hyperglycemia.[128] In addition, some degree of functional insulin deficiency exists [*see Figure 14*].[128] Certain studies suggest that insulin resistance is primary[128,130] and that impaired insulin secretion is only really evident when fasting hyperglycemia supervenes.[128, 131-133] Other investigators find evidence of early abnormal beta cell function in type 2 diabetes mellitus,[134-136] in IGT,[134,137] and in first-degree glucose-tolerant relatives of patients with type 2 diabetes mellitus.[138] Regardless of which comes first, the loss of compensatory beta cell hyperfunction to overcome insulin resistance is a key factor in the progression from genetic susceptibility to established type 2 diabetes mellitus.[139] Furthermore, insulin resistance may cause secondary insulin deficiency, and insulin deficiency tends to lead to insulin resistance; thus, they are mutually reinforcing defects, partly through an effect commonly referred to as glucose toxicity.[140] Some period of hyperglycemia has a secondary noxious effect that aggravates both insulin resistance and insulin deficiency; thus, hyperglycemia begets hyperglycemia. Therefore, any form of treatment of type 2 diabetes mellitus that lowers plasma glucose levels is self-reinforcing and may gain momentum with time by virtue of the added early benefit of eliminating the effects of glucose toxicity. For this reason, aggressive early treatment (e.g., with insulin) can sometimes be replaced with oral drugs or even diet.[141]

The exact locus of insulin resistance in type 2 diabetes mellitus remains unidentified. Indeed, there may be various sites because the disease is considered likely to be a heterogeneous disorder.[142,143] Numerous candidate genes for defective insulin action, including the insulin receptor, glucose transporter, insulin receptor substrate, and insulin target enzymes, such as glycogen synthase, have been largely excluded as common primary causes of insulin resistance[144,145] in type 2 diabetes mellitus.

As in type 1 diabetes mellitus, the loss of effective insulin action directly leads to unrestrained hepatic glucose production and inefficient peripheral glucose utilization [*see Figure 14*]. Exces-

Table 6 Definitions of the Metabolic Syndrome[155,156]

National Cholesterol Education Program Adult Treatment Panel III	*World Health Organization*
At least three of the following:	Diabetes, IGT, or IFG and/or insulin resistance*
Fasting plasma glucose ≥ 110 mg/dl	*plus at least two of the following:*
Abdominal obesity: waist circumference 35 in. in women or > 40 in. in men	Abdominal obesity: waist-to-hip ratio > 0.85 in women or > 0.9 in men and/or body mass index > 30 kg/m^2
Triglycerides > 150 mg/dl; HDL < 50 mg/dl in women or < 40 mg/dl in men	Triglycerides > 150 mg/dl and/or HDL < 40 mg/dl in women or < 35 mg/dl in men
Blood pressure ≥ 130/85 mm Hg	Blood pressure ≥ 140/90 mm Hg
	Microalbuminuria: urinary albumin excretion ≥ 20 µg/min or albumin-to-creatinine ratio ≥ 30 mg/g

*Insulin resistance assessed as fasting insulin ÷ (fasting glucose × 22.5).
HDL—high density lipoprotein IFG—impaired fasting glucose IGT—impaired glucose tolerance

sive hepatic glucose output largely accounts for elevation of FPG levels.[128] Resistance to the antilipolytic action of insulin in adipose tissue leads to elevated plasma free fatty acid (FFA) levels and increased FFA delivery to the liver. There, the oxidation of FFA generates energy (adenosine triphosphate [ATP]) needed to sustain gluconeogenesis; in addition, the latter process is stimulated by FFA metabolites such as acyl coenzyme A (acyl-CoA). In this indirect manner, insulin resistance also contributes to elevated glucose production in the liver.[146] Moreover, the elevation of FFA levels also contributes to insulin resistance in muscle.[147] The presence of some residual insulin secretion in type 2 diabetes mellitus, however, is ordinarily enough to restrain ketogenesis and prevent DKA. Elevated hepatic glucose output largely sustains an elevated FPG, whereas reduced peripheral glucose utilization especially causes elevation of postprandial glucose levels [*see Figure 14*].

The ratio of proinsulin to insulin in plasma is high and remains so even after glucose-lowering therapy,[148,149] suggesting an early abnormality in processing of proinsulin to insulin in the beta cell [*see Figure 3*]. Insulin is normally secreted in cyclic pulses that can be entrained by rapid changes in plasma glucose levels. Disruption of this close concordance between plasma glucose and plasma insulin fluctuations is a subtle lesion that is demonstrable early in patients with type 2 diabetes mellitus and, to a lesser extent, in some patients with only impaired glucose tolerance.[134,136] Finally, the plasma insulin response to abrupt elevation of plasma glucose levels normally shows a first sharp, spikelike phase.[150] Before the plasma insulin level returns to baseline, it slowly rises again to produce a second plateau phase of more prolonged insulin release. The immediate first-phase response to glucose decreases in type 2 diabetes mellitus, as it does in the preclinical phase of type 1 diabetes mellitus, and is completely lost when the FPG level exceeds the normal range.[151]

Other Beta Cell Abnormalities

Another, previously neglected abnormality in type 2 diabetes mellitus is the presence of amyloid in close proximity to the islet beta cells. The amyloid fibrils have been found to contain amylin, a peptide that is cosecreted with insulin.[152] Amylin deficiency parallels insulin deficiency in type 2 diabetes mellitus.[152] Whether the accumulation of amyloid impairs beta cell function or is an epiphenomenon resulting from beta cell hyperfunction with increased amylin secretion in the early phases of the disease remains unclear.

More than 10% of some patient populations presenting with the clinical phenotype of type 2 diabetes mellitus have serum islet cell autoantibodies typical of type 1 diabetes mellitus, such as antibodies to GAD.[153] This combination has been referred to as latent autoimmune diabetes in adults (LADA). These individuals exhibit a rapid decline in beta cell function, as shown by serum C-peptide levels, and they are likely to need insulin replacement therapy, even if their hyperglycemia is initially alleviated by oral beta cell stimulants.[154,155]

Metabolic Syndrome (Insulin-Resistance Syndrome)

The metabolic (insulin-resistance) syndrome is closely associated with, and often a forerunner of, type 2 diabetes mellitus. The metabolic syndrome has been defined both by the National Cholesterol Education Program and the World Health Organization (WHO) [*see Table 6*].[156,157] Only the WHO definition includes insulin resistance per se, assessed by determining the ratio of the fasting plasma insulin level to the glucose level. By either definition, the syndrome represents a collection of risk factors not only for diabetes regulation but also for cardiovascular disease, and it presages both diseases. One obvious link between the components of the metabolic syndrome is obesity, which is a cause of insulin resistance[158] and a contributor to the insulin resistance of type 2 diabetes mellitus.[159] Weight gain presages diabetes,[160] and weight loss in obese individuals prevents progression of IGT to full-blown diabetes.[161] Most patients with type 2 diabetes mellitus have abdominal obesity and many have dyslipidemia, hypertension, and other features of the metabolic syndrome.[129] Abdominal obesity is itself a risk factor for type 2 diabetes mellitus and cardiovascular disease.[162] The interrelationship of the metabolic syndrome, diabetes, and cardiovascular disease is exemplified in the NHANES III study. The overall prevalence of the metabolic syndrome in the United States is 23% in men and women older than 20 years and 44% in those older than 50 years.[163] This huge prevalence of the metabolic syndrome reflects the burgeoning of obesity in the population. In the over-50 age group, 87% of those with diabetes, 71% of those with IFG, and 33% of those with IGT also had the metabolic syndrome.[164] The prevalence of coronary heart disease (CHD) was 8.7% in those with neither diabetes nor the metabolic syndrome and 7.5% in those with only diabetes, but it increased to 13.9% in those with only the metabolic syndrome and to 19.2% in those with both the metabolic syndrome and diabetes. These cross-sectional data suggest that the metabolic syndrome is more potent than diabetes per se as a risk factor for CHD, but hyperglycemia (diabetes) aggravates the risk inherent in the metabolic syndrome. This relation explains much but not all of the vulnerability of patients with type 2 diabetes mellitus to cardiovascular complications resulting from accelerated atherosclerosis. On the other hand, not all patients with the metabolic syndrome and IGT go on to experience full-blown type 2 diabetes mellitus. A large randomized controlled trial is currently testing the ability of lifestyle changes (weight reduction and regular exercise) and the drug metformin to reduce the risk of progressing from IGT to type 2 diabetes mellitus.[165]

Genetic Factors

Type 2 diabetes mellitus has a strong hereditary component. In virtually all monozygotic twinships, the disease develops in both individuals, often within a few years of each other.[166] Offspring and siblings of diabetic patients are at great risk for the disease.

Table 7 American Diabetes Association Plasma Glucose Diagnostic Criteria for Diabetes Mellitus

Diagnosis	*Test Condition*	
	Plasma Glucose (mg/dl)	
	Fasting ≥ 8 hr	*2 hr after 75 g Oral Glucose*
Normal	< 110	< 140
Impaired glucose tolerance (IGT)	< 126	≥ 140–< 200
Impaired fasting glucose (IFG)	≥ 110–< 126	< 200
Diabetes mellitus	≥ 126	—
Diabetes mellitus	< 126	≥ 200
Diabetes mellitus (Classic symptoms + casual plasma glucose, ≥ 200 mg/dl)	—	—
	Plasma Glucose (mg/dl)	
	Fasting	*After 100 g Oral Glucose*
Gestational diabetes mellitus (GDM)	> 105*	1 hr ≥ 190*
		2 hr ≥ 165*
		3 hr ≥ 145*

Note: The Fourth International Workshop-Conference on Gestational Diabetes Mellitus has proposed lower criteria, which would increase the percentage of cases from 4% to 7% in white women. These criteria are fasting, 95; 1 hour, 180; 2 hours, 155; and 3 hours, 140, after 100 g oral glucose.
*Two of these four criteria must be met for diagnosis of GDM.

No HLA markers have been identified for type 2 diabetes mellitus, in contrast to type 1 diabetes mellitus. Most current thinking is that the common forms of type 2 diabetes mellitus represent a complex multigenic disorder. Examination of the mechanism of action of insulin [*see Figure 4*] suggests many logical candidate genes, mutations of which could lead to type 2 diabetes mellitus by causing primary insulin resistance. Thus far, genes for insulin, the insulin receptor, insulin receptor substrate, glucose transporter, protein tyrosine phosphatase (which inactivates the insulin receptor), muscle hexokinase, glycogen synthase, and other insulin target enzymes have all been excluded as the cause of so-called garden-variety type 2 diabetes mellitus.[167] Because of the association with obesity, genes that could cause obesity are also being investigated (e.g., leptin, uncoupling protein, and beta$_3$-adrenergic receptor). The positional cloning approach being used in populations with high diabetes prevalence, such as Pima Indians and Mexican Americans, has yielded hints of loci on certain chromosomes that require confirmation.

There is one form of diabetes, MODY [*see Table 1*], that does have genetic specificity. In this disorder, mutations of several different genes on different chromosomes lead to a common phenotype resembling type 2 diabetes mellitus, but the disorder begins at an early age.[168] One of the genes codes for glucokinase, an enzyme that plays a key role in stimulation of insulin secretion by glucose.[169] Another mutation occurs in a molecule known as insulin production factor–1, a transcription factor responsible for differentiation of precursor cells into beta cells capable of insulin secretion.[168] Two other genes responsible for MODY code for hepatic transcription factor–1 and hepatic transcription factor–4, which, despite their names, operate in beta cells to regulate the glucose responsive pathway of insulin secretion.[168] All of these genetic abnormalities more likely explain type 2 diabetes mellitus caused by beta cell dysfunction than that caused by peripheral insulin resistance. Their functional relation to the diabetic diathesis is still obscure. Even in a phenotypically well defined monogenic form of diabetes such as MODY, the existence of many alleles for hepatic transcription factor–1 indicates the genetic complexity of diabetes. Although the mutations responsible for MODY account for only a minute fraction of all cases of type 2 diabetes mellitus, they encourage the view that genes contributing to most or all cases of type 2 diabetes mellitus will eventually be found.

IMPAIRED GLUCOSE TOLERANCE

The state known as IGT [*see Table 7*] is associated with a future risk of development of diabetes of 1% to 10% a year, with different levels of risk for different ethnic groups. Equally important is the association of IGT with the metabolic syndrome [*see Table 6*], which includes hyperinsulinemia, glucose intolerance, dyslipidemia, hypertension, and impaired fibrinolysis. Presence of this syndrome constitutes a high risk for atherosclerosis, cardiovascular disease, thrombotic events, and mortality. The category of impaired fasting glucose was established by the American Diabetes Association as an intermediate zone between the upper limit of normal and the lower limit for diabetes.[1] IFG is also associated with increased risk of diabetes and cardiovascular disease. IFG and IGT are not identical states. About one third of people with IGT have IFG, one third of those with IFG have IGT, and one third of affected individuals have both.[2] The pathophysiologic bases and clinical significance of the differences between IFG and IGT remain to be determined. Both conditions can be thought of as early stages of type 2 diabetes mellitus and can be referred to as prediabetes.

PREVENTION OF TYPE 2 DIABETES

Five randomized clinical trials have recently demonstrated that the risk of progression from IGT to diabetes can be significantly reduced by lifestyle modifications or pharmacologic interventions. The Diabetes Prevention Program (DPP),[170] the Finnish Diabetes Prevention Study,[171] and the Da Qing IGT and Diabetes Study[172] showed that intensive diet and exercise therapy brought reductions ranging from 42% to 58% in the progression from IGT to diabetes over 3 to 6 years. The weight loss achieved and the amount of exercise performed were modest—5.6 kg and 150 minutes of brisk walking a week in the DPP. The DPP also had a placebo-controlled metformin (850 mg twice daily) treatment arm, which showed a 31% reduction in diabetes. Most of this effect persisted after a 1-week washout from metformin. In the STOP-NIDDM trial, 100 mg of acarbose three times daily, compared with placebo, reduced diabetes development by 25%.[173] Finally, in a group of Hispanic women with previous gestational diabetes, 400 mg of troglitazone daily, compared with placebo, reduced development of diabetes.[174] This benefit was still present after an 8-month drug washout.

The efficacy, safety, and consistency of lifestyle interventions are impressive, but long-term follow-up is needed to determine how long such patients will continue to implement this therapy and how durable the benefits will be from either lifestyle changes or drugs. Equally important is whether car-

diovascular disease events will be reduced eventually. A preliminary report from the first 3 years of the STOP-NIDDM trial suggests an encouraging significant reduction in myocardial infarction and total cardiovascular disease events.[175]

DIAGNOSIS OF TYPE 2 DIABETES MELLITUS

Although patients with type 2 diabetes mellitus may present with symptoms as florid as those of type 1 diabetes mellitus (but usually not exhibiting spontaneous ketonuria), most patients with type 2 disease have relatively mild polyuria and polydipsia, and many cases are diagnosed only by office screening or other health checks.

The preferred test for type 2 diabetes mellitus on the grounds of reproducibility, convenience, and cost is an FPG . Oral glucose tolerance testing (OGTT) is more sensitive than FPG but is not recommended for routine use, because it is less reproducible, more inconvenient, and more costly.[1] Moreover, the recommended treatment for almost all overweight or obese patients who would be candidates for OGTT would be the same regardless of OGTT results: a combined regimen of nutrition therapy, weight loss, and exercise. OGTT may be considered in unusually high risk patients and in those with IFG.

MANAGEMENT OF TYPE 2 DIABETES MELLITUS

The same glycemic goals discussed earlier [*see Table 5*] are appropriate for type 2 diabetes mellitus. However, these goals may sometimes have to be modified if severe cardiovascular disease, concurrent life-shortening malignancy, hypoglycemia unawareness, or inadequate family or social support make intensive treatment of diabetes dangerous or unlikely to benefit the patient in the long run. Self-monitoring of blood glucose when patients with type 2 diabetes mellitus are treated with diet plus exercise or with oral drugs is of less well established utility in patients with type 2 diabetes mellitus than in patients with type 1 diabetes mellitus. However, fasting and postprandial blood glucose levels both correlate with HbA_{1c} levels, and postprandial values can help reveal inadequate attention to diet and insufficient effectiveness of certain oral agents.

Nutritional Therapy and Exercise

An excellent short-term glycemic response to caloric reduction in patients with type 2 diabetes mellitus who are even modestly overweight can be expected.[175, 176] On the basis of the degree of obesity and with the help of a dietitian, the patient should be provided with individualized culturally appropriate instructions to reduce intake by at least 250 to 500 calories a day. Such a decrease generally leads to an overall weight loss of 0.5 to 1.0 lb a week. There should be periodic reinforcement by the dietitian and physician. In the absence of a dietitian, the patient's basal metabolic rate can be estimated at 10 cal/lb (20 cal/kg) of ideal body weight. A caloric prescription less than this amount will perforce decrease energy intake below the total daily energy expenditure. Consensus guidelines recommend that the calories should consist of less than 30% total fat, less than 10% saturated fat, less than 10% polyunsaturated fat, 10% to 15% monounsaturated fat, 10% to 20% protein, and 50% to 55% carbohydrate.[177] Table sugar and other concentrated forms of carbohydrates are allowable in small portions at any one time (e.g., 5 g or 1 tsp of table sugar). Adding high-fiber foods can also lower plasma glucose modestly.[178] Teaching patients to count the contemplated grams of carbohydrate before each meal helps them limit elevation of postprandial plasma glucose (PPG).

In massively obese individuals with BMI greater than 40 who are very symptomatic from hyperglycemia, a very low calorie diet (400 to 800 total calories a day using special high-protein supplements) can be very effective for the initial 2 to 3 months, but this strategy requires close medical monitoring.[179]

Weight losses of 5% to 10% (10 to 20 lb) produce significant decreases in FPG and HbA_{1c} over 1 to 3 months.[176] In the UKPDS, mean HbA_{1c} fell from 9% to 7% during the 3-month dietary run-in period before randomization of the study patients.[180,181] However, many patients are unable to maintain a calorie-restricted diet and even their initial weight loss. Pharmacologic aids for weight loss can be considered in such cases, but their efficacy is limited. These drugs include orlistat,[182] a gastrointestinal lipase inhibitor that causes malabsorption of fat calories, and sibutramine, an inhibitor of dopamine, norepinephrine, and serotonin reuptake. Even after the addition of a weight-loss drug to therapy, appropriate diet therapy is essential. The patient should not be blamed for recidivism, because inability to lower body weight to ideal and keep it there may well be a central nervous system manifestation of or contributor to type 2 diabetes mellitus and out of the patient's consistent control.[183] Surgical therapy for obesity by reduction of gastric volume[184,185] can effectively control type 2 diabetes mellitus and is gaining acceptance in very obese individuals who are unresponsive to other therapy. Of great interest, such treatment may work by altering the concentrations of humoral signals from the gastrointestinal tract that regulate appetite.

Additional benefits accrue from gradually increased aerobic exercise[186] aimed at achieving at least 60% of maximal heart rate (220 minus age), such as walking 45 minutes at a brisk pace (approximately 3 to 5 miles an hour) three to five times a week. Exercise decreases insulin resistance and glycemia, contributes modestly to weight loss, reduces the risk of future cardiovascular disease, improves prognosis should a myocardial infarction occur, and enhances the patient's sense of well-being and physical fitness. Conversely, physical inactivity predicts mortality in men with type 2 diabetes mellitus.[187] In the presence of known coronary artery disease (CAD), the exercise should be prescribed with input from the patient's cardiologist. If type 2 diabetes mellitus has existed for more than 5 to 10 years or if the patient already has peripheral vascular or cerebral vascular disease, autonomic neuropathy, microalbuminuria, dyslipidemia, or a history of smoking, an electrocardiogram is essential and an electrocardiographic exercise tolerance test is prudent before initiating a formal exercise program.

Pharmacologic Monotherapy

The array of pharmacologic agents available for treatment of type 2 diabetes mellitus is increasing steadily. Drugs can be specifically directed at the known pathophysiologic defects in type 2 diabetes mellitus [*see Figure 15*]. Although patient compliance favors initial use of monotherapy, none of the available agents can alone be expected to adequately control hyperglycemia indefinitely.[188] Therefore, diabetologists are beginning to consider using combinations of drugs from the outset of the need for any pharmacotherapy.[189] Clinical trial data have established the efficacy and safety of various drugs [*see Table 8*] . The degrees to which these drugs lower HbA_{1c} are fairly similar; the higher the initial dose of these agents, the greater the decrease in HbA_{1c}.

Sulfonylurea agents SU agents, the oldest oral hypoglycemic drugs, continue to have an important place in treat-

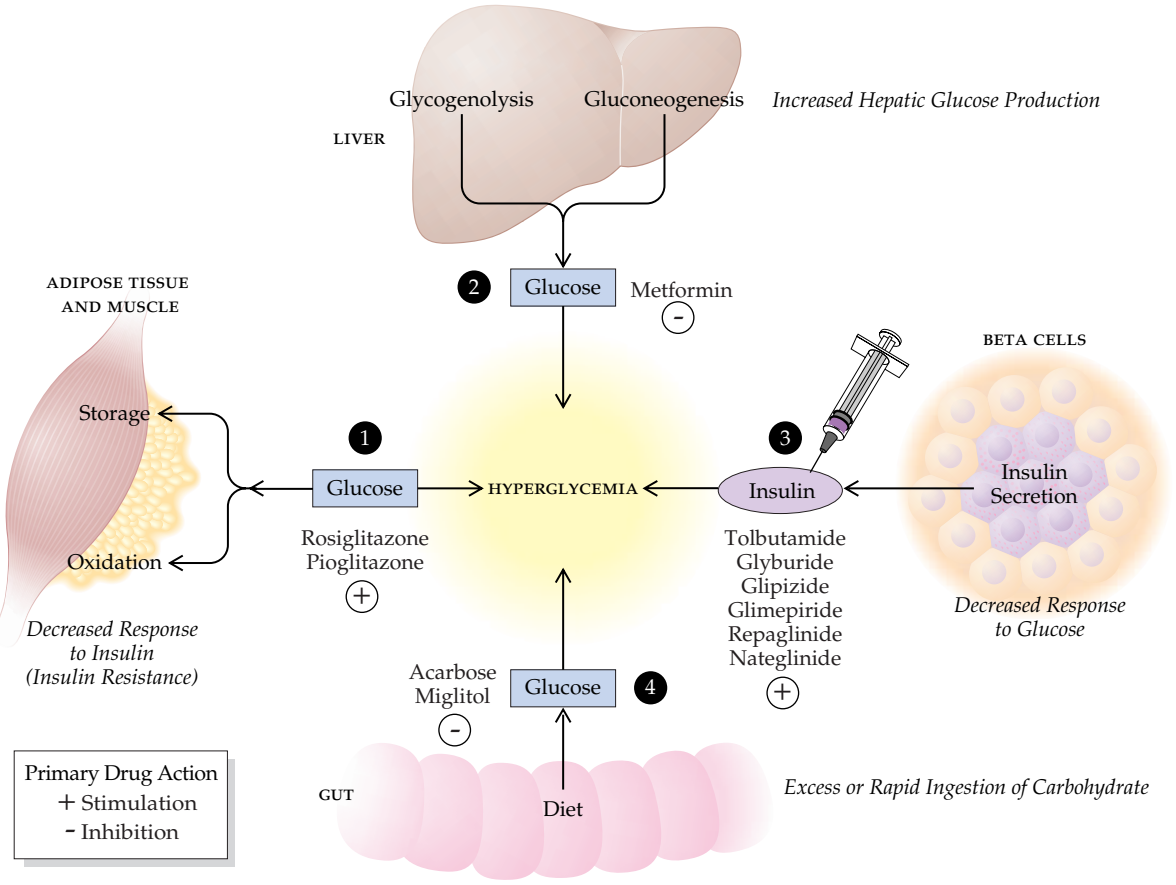

Figure 15 **Multiple drug classes with different predominant therapeutic effects are available for use singly or in numerous combinations. (1) Glitazones (thiazolidinediones) increase the sensitivity to insulin of glucose uptake by muscle and adipose tissue. (2) Metformin, the only approved biguanide drug, inhibits glucose production by the liver. (3) Sulfonylureas, repaglinide, and nateglinide stimulate insulin secretion, and insulin itself can be provided by injection. (4) α-Glucosidase inhibitors slow the digestion and absorption of carbohydrates from the diet. Plus signs indicate stimulation. Minus signs indicate inhibition.**

ment. Their primary mechanism of action is to close ATP-sensitive potassium channels in the beta cell (and other cell) membranes, which leads to an influx of calcium and stimulation of exocytosis of insulin storage granules. They are most effective in normal-weight or modestly obese individuals who have had diabetes for less than 5 years and who can still secrete considerable amounts of insulin. The SU drugs in common use stimulate the beta cells more or less continuously and secondarily decrease insulin resistance. These effects [*see Figure 14*] result in decreases in FPG of 50 to 70 mg/dl and HbA_{1c} of 1.0% to 2.0%.[190] Peak PPG levels fall approximately as much as FPG. For most patients, treatment is initiated with the lowest recommended dose, and the dose is increased every 1 to 2 weeks until target blood glucose levels are attained or a practical maximal dose is reached [*see Table 9*]. Modern SU drugs can be taken as a single daily dose but occasionally are more effective when split into twice-daily doses. In symptomatic patients with FPG greater than 250, the patient may begin with half the maximal recommended dose. Hypoglycemia, in particular, and weight gain are adverse effects of SU drugs. The highest prevalence of hypoglycemia occurs with glyburide and chlorpropamide,[191] drugs with long biologic half-lives. Elderly patients who live alone and lack concerned family, friends, or neighbors are at a special risk for severe, even fatal, hypoglycemia.[192] The shortest-acting SU drug, tolbutamide, may be the safest to use in such cases.

Patients who present to an emergency room in hypoglycemic coma from any SU drug should be given restorative treatment with intravenous boluses of glucose and then admitted to the hospital because SU drugs can have durations of biologic action for up to 7 days. A blood glucose should be maintained at 150 to 200 mg/dl on intravenous glucose, oral carbohydrate, or both until this level can be sustained by administration of only 5 g/hr of one of the therapeutic agents. In the UKPDS, SU drugs did not increase cardiovascular disease events or mortality.[37] This observation relieves much of the concern previously raised by the University Group Diabetes Program trial in 1970, which found that tolbutamide was associated with an excess of cardiovascular and total deaths.[193] However, interactions of even modern SU drugs with cardiac muscle are reported, particularly inhibition of ischemic preconditioning, a cardioprotective mechanism.[194] SU drugs are contraindicated in hepatic insufficiency and are dangerous when combined with alcohol ingestion. Glimepiride, the newest SU drug,[195] has been given safely to patients with renal insufficiency, although these patients are susceptible to hypoglycemia for other reasons. SU drugs are subject to interactions with other drugs that can either exaggerate or interfere with their effects.

Beta cell stimulants Repaglinide and the phenylalanine derivative nateglinide represent a new class of beta cell stimulants [*see Figure 15*] that differ in structure and timing of action

Table 8 Oral Drugs for Type 2 Diabetes Mellitus

Drugs	*Lowest Effective Single Dose (mg)*	*Practical Maximum Daily Dose (mg)*	*Hypoglycemia with Monotherapy*
Sulfonylureas*			
Glyburide	1.25	10	Yes
Micronized glyburide	1.5	6	Yes
Glipizide	5	20	Yes
Glipizide (gastrointestinal therapeutic system)	5	20	Yes
Glimepiride	0.5	8	Yes
Meglitinides†			
Repaglinide	0.5	4‡	Yes
Biguanides			
Metformin	500	2,000	No
Thiazolidinediones§			
Rosiglitazone	2	8	No
Pioglitazone	15	45	No
α-Glucosidase inhibitors			
Acarbose	25	100‡	No
Miglitol	25	100‡	No

*Tolbutamide, chlorpropamide, and acetohexamide are also still available.
†Nateglinide has a similar action to meglitinides but is technically phenylalanine derivative.
‡This maximal dose must be taken each time with meals.
§Troglitazone was the initial drug approved in this class but was later withdrawn because of serious liver toxicity.

from those of SU drugs.[196] Although they may act in part through SU drug mechanisms in the beta cells,[197] they do so rapidly, with a peak effect at about l hour, and transiently, with a duration of about 4 hours. Their major action is the decrease of PPG by 50 to 60 mg/dl, although FPG also declines somewhat as glucose toxicity is relieved. As monotherapy, these new beta cell stimulants are most logically used early in type 2 diabetes mellitus, when FPG is not greatly elevated. They lower HbA_{1c} by about 1.0%. Repaglinide and nateglinide must be taken 15 to 30 minutes before a meal and should never be taken without eating. Their short half-lives and the fact that, unlike SU drugs, they are active only in the presence of glucose are expected to reduce the likelihood of severe prolonged hypoglycemic episodes.[196] Weight gain may occur secondary to improved glycemic control.

Table 9 Combination Oral Drug Therapy for Type 2 Diabetes Mellitus

Combinations reported in the literature
- Sulfonylurea + metformin
- Sulfonylurea + thiazolidinedione
- Metformin + thiazolidinedione
- Metformin + repaglinide
- Repaglinide + thiazolidinedione
- Sulfonylurea + metformin + thiazolidinedione
- Acarbose + any other drug except repaglinide
- Miglitol + sulfonylurea
- Insulin + any other drug

Potentially useful combination
- Repaglinide + metformin + thiazolidinedione
- Nateglinide + metformin + thiazolidinedione

α-Glucosidase inhibitors α-Glucosidase inhibitors[197,198] are a class of drugs represented by acarbose and miglitol, which are poorly absorbed but act within the gut to inhibit the digestion of polysaccharides [*see Figure 15*]. This action results in a slow release of glucose from food and therefore slow absorption from the GI tract. PPG levels decrease by 60 to 70 mg/dl, but FPG decreases by only 15 to 20 mg/dl.[199] HbA_{1c} generally falls 0.5% to 0.8%.[198,199] These drugs are useful only as monotherapy when postprandial hyperglycemia is the main problem. They must be taken at the start of a meal. Flatulence, abdominal cramping, and diarrhea are frequent side effects that result from undigested carbohydrate reaching bacteria in the lower bowel. These side effects often limit patient acceptance of treatment with α-glucosidase inhibitors. Treatment should start with the smallest dose, and doses should be raised very gradually to enhance tolerance. With the exception of rare elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, these agents are nontoxic. Although hypoglycemia does not occur with monotherapy, it can do so when α-glucosidase inhibitors are added to SU drugs or insulin. In those instances, patients must be warned to treat hypoglycemia only with pure glucose (e.g., glucose tablets) because the therapeutic benefits of complex carbohydrates and even sucrose will be delayed by slow digestion.

Biguanide agents Metformin,[200] the only drug approved in the biguanide class, acts primarily by decreasing excessive hepatic glucose production [*see Figure 15*],[201,202] most likely through inhibiting gluconeogenesis. Because insulin also inhibits gluconeogenesis [*see Figure 1*][20] and metformin requires the presence of insulin to be effective, metformin may be considered a hepatic insulin sensitizer. During metformin treatment, plasma insulin levels tend to decrease relative to glucose levels as a result of the decrease in insulin resistance. The chief action of this drug is to lower FPG by 50 to 70 mg/dl, with peak PPG levels following

suit.[203] Hypoglycemia almost never occurs with metformin monotherapy. Weight is not gained and may even be lost.[200] Metformin also decreases plasma triglyceride and low-density lipoprotein (LDL) cholesterol levels, and it increases HDL cholesterol levels to some degree. In addition, plasma plasminogen activator inhibitor–1 (PAI-1) activity declines.[204] The weight loss, the improvement in the dyslipidemia typical of type 2 diabetes mellitus, and the reduction in antifibrinolytic activity could explain one of the most interesting UKPDS observations. Compared with conventional diet treatment, metformin monotherapy substantially decreased the incidence of myocardial infarction, diabetes-related death, and all-cause mortality in an obese type 2 subcohort of the trial.[38]

The most common side effects of metformin therapy are diarrhea, which may be severe; abdominal cramps; and gastric upset. To reduce the likelihood of these symptoms, the starting dose should not exceed 500 mg twice a day, and the drug should be used with special caution, if at all, in patients who have inflammatory GI disease. The maximum effective dose is 2,000 mg/day.[205] The most feared, although rare, adverse effect is lactic acidosis.[206] This often fatal complication occurs in 30 per million patients a year, and it usually occurs when the drug is used inappropriately, such as when the serum creatinine level is elevated or the patient is dehydrated. Hemodialysis along with bicarbonate administration can be effective therapy for metformin-induced lactic acidosis.[207] The following are contraindications to use of metformin: serum creatinine level greater than 1.4 mg/dl in women and greater than 1.5 mg/dl in men; intravenous administration of radiographic iodinated contrast media; acute myocardial infarction; congestive heart failure; and any ischemic condition. Nausea, vomiting, tachypnea, and change in mental status call for measurements of serum electrolytes and lactate to rule out lactic acid metabolic acidosis. Although metformin monotherapy can be effective in both normal-weight and obese patients with type 2 diabetes mellitus, obese patients especially benefit from metformin therapy because of the absence of weight gain as glucose levels gradually fall.

Thiazolidinediones The newest class of oral drugs are thiazolidinediones (TZDs) [*see Table 8*],[208] which were exemplified by the no longer available but best studied drug, troglitazone . These agents work predominantly in muscle and adipose tissue to decrease insulin resistance [*see Figure 15*].[202,209] Because insulin resistance is seen in almost all patients with type 2 diabetes mellitus, the advent of the TZDs raised expectations that they might be singularly effective. Like metformin, TZD drugs need the presence of insulin and are especially effective in obese patients. They also decrease hepatic glucose production to some extent.[202] As monotherapy, they decrease FPG by 50 to 70 mg/dl and PPG by slightly more than that.[209] HbA_{1c} decreases by about 1.0% to 1.5%. Plasma insulin levels also decrease as glucose levels fall.[209] TZD drugs act by binding to a metabolically important receptor, the peroxisome proliferator-activated receptor (PPAR), and they thereby regulate the expression of multiple genes.[210] Their clinical effects take 4 to 12 weeks to become evident. In patients with marked elevation of FPG, a midrange dose is appropriate to start with (e.g., 4 mg rosiglitazone or 30 mg pioglitazone). Otherwise, the lowest dose is appropriate, and dose changes should be made at 4- to 12-week intervals.

TZD drugs can cause weight gain, which is partly fat tissue and partly extracellular fluid.[208] The accumulation of extracellular fluid presents as edema, which can be troublesome when concurrent congestive heart failure exists, and a small dilutional fall in hemoglobin and hematocrit. Some findings suggest that the adipose tissue gain is largely subcutaneous rather than visceral.[211] In clinical research trials, troglitazone therapy was accompanied by elevations of ALT and AST to more than three times the upper limit of normal in 2% of treated patients, compared with 0.6% of patients given placebo. However, after troglitazone was approved by the FDA, more than 60 cases of hepatic failure that necessitated liver transplantation or resulted in death, or both, were reported out of a user base of about one million persons. The FDA eventually withdrew approval, first for the prescription of troglitazone as monotherapy and later for all indications. In clinical research trials, neither rosiglitazone nor pioglitazone caused AST and ALT elevations in excess of those caused by placebo, but these drugs have not been used enough to provide a guarantee that they will never cause idiosyncratic liver toxicity similar to that caused by troglitazone. Therefore, the FDA has mandated that these drugs be monitored by ALT measurements every 2 months for the first year of use. Neither rosiglitazone nor pioglitazone should be prescribed if the ALT level is greater than 2.5 times the upper limit of normal, and the drugs should be stopped if such levels are reached.

TZD drugs have exhibited effects in addition to glucose lowering that may be beneficial for treating cardiovascular complications.[212-219] Troglitazone and pioglitazone suppress formation of PAI-1, an action that enhances fibrinolysis.[213,214] TZD drugs tend to decrease serum triglyceride levels and increase serum HDL cholesterol levels, but they also increase serum LDL cholesterol levels.[208] In addition, troglitazone has been reported to shift the LDL spectrum from small, dense atherogenic particles to larger, more buoyant, less atherogenic particles.[219] Endothelial function also likely improves.[216,217] A decrease in carotid artery intimal-medial thickness[217]—a marker of atherosclerosis—as well as decreases in vasospastic angina[215] and in recurrence of intimal hyperplasia after coronary angioplasty[218] have been reported in small series of patients treated with troglitazone for only 6 months.[216,217] Whether TZD drugs will decrease rates of cardiovascular events through such actions remains to be seen.

Insulin About 40% of patients with type 2 diabetes mellitus in the United States are estimated to be taking insulin. A small proportion of these patients may have delayed-onset type 1 diabetes mellitus and may offer serologic evidence of beta cell autoimmunity. However, most of these patients represent the end stage of type 2 diabetes mellitus. A small number of such patients, some of whom are even obese, present initially with clear-cut biologic evidence of insulin deficiency. This evidence includes marked recent loss of weight and muscle mass, debilitating fatigue and weakness, severe polyuria and polydypsia, considerable hypertriglyceridemia, ketonuria, and FPG often exceeding 300 mg/dl. These patients should be started on insulin immediately—as in patients with type 1 diabetes mellitus. After usually rapid clinical and biochemical improvement, insulin-dose requirements may decrease progressively. Patients can sometimes be tapered off insulin and be given a trial of an SU drug. This sequence has been reported in certain groups of African Americans.[220,221]

Much more commonly, the need for insulin treatment has arisen because of eventual failure of oral drug therapy, particularly SU drugs. For normal-weight individuals in this situation, it is best to simply switch them to insulin. Some patients may still be managed on a single dose of intermediate- or long-acting insulin (starting dose of NPH, Lente, or glargine of 0.15 to 0.20 U/kg) in

the morning[222] or at bedtime if the FPG is being specifically targeted.[223] The latter is a particularly attractive way to lessen glycemia without stimulating weight gain.[224] Other patients may need intermediate- or long-acting insulin twice a day, usually in a ratio of breakfast dose to bedtime dose of from 1:1 to 2:1. As endogenous postprandial insulin secretion declines further, regular or lispro insulin or insulin aspart [*see* Type 1 Diabetes Mellitus, *above*] must be added before meals. To approach normal glycemia, the doses of rapid, short-acting insulin are best adjusted according to the premeal blood glucose level, the carbohydrate content of the meal, or both. For all practical purposes, some patients with type 2 diabetes mellitus closely resemble patients with type 1 diabetes mellitus in the insulin regimens they require.

For stable patients incapable of accurately mixing different insulins in one syringe because of visual or cognitive impairment, premixed combinations of NPH with regular or lispro insulin are available in varying proportions; these combinations include 70% NPH/30% regular, 50% NPH/50% regular, and 75% NPH/25% lispro. These mixtures all suffer from the inflexibility of neither the dose of NPH nor the dose of the regular or lispro insulin being able to be altered individually. For example, a patient with satisfactory postbreakfast or prelunch blood glucose levels but elevated predinner blood glucose levels would benefit from an increase in the morning NPH insulin dose but not necessarily from an increase in the morning regular or lispro insulin dose. Premixed insulins are not suitable for bedtime use unless an uncommonly large snack is eaten. Despite the above objections, premixed insulins are convenient for patients and for family members who have therapeutic responsibilities.

Whatever insulin regimens are chosen, obese patients with type 2 diabetes mellitus often need large daily doses, which many practitioners are unaccustomed to prescribing. Doses of 1 U/kg body weight are not unusual, and doses of up to 400 U daily have been required to achieve glycemic targets in morbidly obese individuals.[225,226] Concern has been raised in the past that insulin might have atherogenic effects because epidemiologic studies (mostly in nondiabetic individuals) have shown an association between insulin resistance, fasting or postprandial plasma insulin levels, and future risk of cardiovascular disease.[227] In the UKPDS[37] and in the University Group Diabetes Program,[228] exogenous insulin did not increase the rate of myocardial infarction or of cardiovascular death. It can be argued that the insulin doses used in those trials were not very large or that an adverse effect from an atherogenic property of insulin was offset by a beneficial effect resulting from a decrease in glycemia. In any event, there is not enough evidence of cardiovascular danger from exogenous insulin to justify withholding doses necessary to achieve near-normal glycemia. In two randomized clinical trials[37,229] and in a large retrospective study,[192] the incidence of serious hypoglycemic episodes was about two to three events per 100 patient-years. In elderly patients, however, one out of 20 severe hypoglycemic events can be accompanied by such complications as stroke, transient ischemic attack, myocardial infarction, injury, and death.[190] Weight gain—in rare cases, even to degrees that have resulted in sleep apnea—is a major adverse effect of insulin therapy and is one justification for combining insulin with a drug such as metformin, which can restrict weight gain to some extent.[230]

Combination Therapy

Improved understanding of the pathogenesis of hyperglycemia in type 2 diabetes mellitus and longer experience with oral drug monotherapy have greatly increased interest in and popularity of using combinations of oral drugs. In patients with considerable hyperglycemia, none of the current drugs reliably normalize HbA_{1c} when used alone, probably because they act primarily by correcting single abnormalities [*see Figure 15*]. Thus, to reach aggressive therapeutic targets [*see Table 3*], combinations are needed [*see Table 9*]. Moreover, all forms of monotherapy—including insulin used conventionally—fail after a number of years, with the possible exception of TZD drugs, for which long enough experience is still lacking. This need for combination therapy was best shown by the UKPDS experience.[37,188] Combination therapies attack two or more different causes of hyperglycemia simultaneously—for example, reducing insulin resistance in the liver with metformin while increasing insulin secretion with an SU drug[203] or meglitinide.[231] Moreover, as a practical matter, when monotherapy fails after initial success, substituting another drug from a different drug class has not been effective (except for insulin), as has been shown in trials that unsuccessfully attempted to substitute metformin[203] or a TZD drug[232] for an SU drug. By contrast, addition of either metformin[203] or a TZD[232] to an SU drug did lower HbA_{1c} significantly. The combinations of metformin with repaglinide,[231] metformin with a TZD drug,[202] and repaglinide with a TZD drug[233] have also been more effective than any of these agents given alone. Pharmaceutical companies have responded to these considerations by marketing combination pills containing metformin and either glyburide or rosiglitazone for use as initial drug therapy. The single tablet may improve compliance with a two-drug regimen.

α-Glucosidase inhibitors complement the different actions of each of the other drugs, including insulin,[198] and their combinations. All other oral drugs are effective when added to SU drugs, except possibly repaglinide or nateglinide, for which data are still lacking. Metformin and a TZD drug also work in triple combination with an SU drug or meglitinide. Combinations of oral drugs may at least postpone having to switch the patient to progressively more intensive insulin therapy as last recourse. Furthermore, the progressive rise in plasma glucose levels seen in patients on monotherapy in the UKPDS was attributable to declining beta cell function.[234] Thus, pathophysiologically rational combinations of oral drugs, if used much earlier in patients with type 2 diabetes mellitus, might even preserve beta cell function longer than was previously achieved with the initial monotherapy approach.

When adding drugs, particularly to insulin, it is usually wise to start with the lowest dose of the drug being added to the regimen and to increase the dose as though it were being used as monotherapy. Self–blood glucose testing at times of the day appropriate for the added drug should be used as a safety check and a guide to efficacy. For metformin, TZD drugs, SU drugs, and bedtime insulin, the FBG is especially helpful. For repaglinide, nateglinide, α-glucosidase inhibitors, premeal regular insulin, lispro insulin, or insulin aspart, postprandial blood glucose levels are important guides to therapy. Patients should be given blood glucose guidelines for when to call the physician (e.g., when FBG is consistently less than 100 mg/dl).

Combination therapy can be quite expensive, even when it results in a lower insulin requirement.[235] The primary aim should always be to decrease the HbA_{1c}. Reduction in insulin dose, number of injections, or both should be thought of only as a secondary benefit.

MANAGEMENT OF HYPEROSMOLAR HYPERGLYCEMIC NONKETOTIC COMA

Type 2 diabetes mellitus seldom gives rise to DKA unless the patient experiences a severe medical stress. On the other hand,

hyperosmolar hyperglycemic nonketotic coma (HHNC) is a common and feared acute complication characterized by extreme hyperglycemia (> 600 mg/dl) and serum hyperosmolarity (> 320 mOsm/L) but with little or no ketosis.[110,236,237] The CNS effects of extreme hyperosmolarity range from somnolence or confusion to coma but notably can also include focal or generalized seizures as well as focal neurologic deficits that disappear with treatment. The absence of severe ketonemia is usually attributed to enough residual insulin secretion that lipolysis is not as unrestrained as in type 1 diabetes mellitus with DKA. HHNC is marked by extreme dehydration, in which the deficit of free water is prominent and the circulatory volume is often seriously compromised. Thus, hypotension; extemely dry skin and mucous membranes; and gross elevation of hematocrit, urea nitrogen, creatinine, and albumin are frequent. Secondary lactic acidosis[110] is not uncommon, so that the serum bicarbonate level may be low and the anion gap increased. The increased viscosity of the blood predisposes to thrombotic events in the cerebral and coronary artery circulations. However, stroke and myocardial infarction, along with pancreatitis and sepsis, may also precipitate the syndrome. It has also been caused by drugs such as hydrochlorothiazide, phenytoin, and glucocorticoids. Elderly patients living in nursing homes are particularly vulnerable to HHNC because their thirst mechanisms are less sensitive to a rising serum osmolality and because dementia, increasing obtundity, or institutional conditions may combine to reduce water intake to less than urinary and insensible water losses. At presentation, serum sodium level is usually elevated or surprisingly normal in the face of extreme hyperglycemia (i.e., the expected pseudohyponatremia is absent). Whatever the presenting level of serum sodium is, it will rise, sometimes markedly, when glucose levels decline with insulin treatment.

Fluid replacement is the most important component of therapy. Restoration of circulating volume is an urgent first priority. One to two liters of isotonic 0.9% saline is therefore given rapidly initially, followed by 0.45% saline. Later, when plasma glucose levels have declined to 250 to 300 mg/dl, 5% glucose in water or in 0.2% saline is given. Total fluid deficits of as much as 12 L may have to be replaced. Insulin treatment, as for DKA, is started after at least 1 or 2 L of 0.9% saline has been administered. Potassium must be added to intravenous fluids to prevent hypokalemia caused by insulin action. It may take days of fluid replacement, the tonicity of which must be carefully adjusted to achieve a gradual steady decrease in serum osmolality and sodium levels, before central nervous system function returns to normal or at least to baseline. The mortality in HHNC is still high. Infection, especially of the urinary tract, even if only suspected, should be treated with broad-spectrum antibiotics. Papillary necrosis may be seen. Patients with histories of arterial and venous thrombosis can benefit from low-dose prophylactic heparin administration.

Cardiovascular Complications of Diabetes Mellitus

Diabetes as an independent risk factor for cardiovascular disease[238] in women is now well established and is so great that it equalizes the risk of cardiovascular disease in men.[239] The risk of a first myocardial infarction in patients with diabetes is equal to that in nondiabetic individuals who have already suffered such an event.[240] Furthermore, acute and subsequent mortality is greater with diabetic-related myocardial infarctions than with nondiabetic myocardial infarctions.[241] In type 1 diabetes, cardiovascular disease is often a fatal accompaniment of end-stage renal disease (ESRD),[242] although even in patients without ESRD, cardiovascular complications may occur earlier in life than usual. Cardiovascular complications are the most prominent cause of morbidity and the most frequent cause of mortality in type 2 diabetes mellitus.[243,244] Mortality in individuals with diabetes is higher than that in nondiabetic persons of all age and racial groups and both sexes.[244] The decline in heart disease mortality noted in recent years in the United States was less in diabetic persons than in nondiabetic persons, and mortality even increased in women with diabetes.[245] The same common cardiovascular disease risk factors important in nondiabetic individuals are clustered in individuals with type 2 diabetes mellitus[129] as part of the metabolic syndrome. The pathologic picture of atherosclerosis in diabetic persons is similar to that in nondiabetic individuals, and the same processes lead to ischemic events. Thus, in regard to cardiovascular disease, the difference between diabetes and nondiabetes appears largely quantitative, although diabetes remains an independent risk factor even after adjusting for other known risk factors.[238]

Intensive treatment of type 1 or type 2 diabetes mellitus to achieve near-normal glycemia has not been proved to reduce the incidence of cardiovascular complications. The UKPDS reported that intensive treatment with insulin or SU drugs decreased myocardial infarction by 16%, with a *P* value of less than 0.052.[37] Data from several populations,[246-249] and the UKPDS[250] have shown that HbA_{1c} is a risk factor for cardiovascular events and death. Randomized clinical trials are under way to test the question of whether improved glycemic control or particular blood glucose lowering strategies will decrease cardiovascular outcomes in various stages of type 2 diabetes mellitus. Because we still cannot always eliminate whatever risk is incurred from hyperglycemia or insulin resistance per se, we must work assiduously to minimize or negate the adverse effects of hypertension, dyslipidemia, smoking, obesity, and physical inactivity on the cardiovascular system.

HYPERTENSION

Aggressive treatment of hypertension in diabetes mellitus is mandatory for three important reasons: (1) it decreases the risk of cardiovascular disease and mortality,[251] (2) it reduces or at least delays progression of diabetic nephropathy to ESRD,[252-254] and (3) it may decrease the risk of hemorrhage from proliferative retinopathy. The most recent American Diabetes Association guidelines[81] recommend a target blood pressure of 130/80 mm Hg, equivalent to a mean blood pressure of 97 mm Hg (mean blood pressure is easily calculated as one third systolic plus two thirds diastolic). However, even lower blood pressure targets may eventually prove to be advisable.

ACE inhibitors have enjoyed first-choice status in treatment because even in nonhypertensive diabetic patients, these agents decrease albumin excretion and the rate of decline in glomerular filtration rate.[254,255] Similar benefits are offered by angiotensin receptor blockers (ARBs)[256-258]; the ARB losartan also decreased cardiovascular disease events more than did the beta blocker atenolol.[259] Low-dose diuretics (chlorthalidone or hydrochlorothiazide) and beta blockers are also very effective antihypertensive agents in diabetes; they decrease risks of cardiovascular disease events and mortality as well as renal failure. However, the possible adverse effects of these agents on glycemic control and serum lipids must be monitored. Atenolol and captopril were equally effective in lowering blood pressure and reducing cardiovascular events and death in the UKPDS.[260] In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[261] which included approximately 12,000 diabetic patients, 12.5 to 25 mg of chlorthalidone was at least as effective

as lisinopril and amlodipine in blood pressure reduction and was associated with equal rates of nonfatal myocardial infarction and CHD. However, the cheaper chlorthalidone was superior to the other two agents in preventing heart failure and was superior to the ACE inhibitor lisinopril in preventing strokes and a combined cardiovascular disease end point. The role of calcium channel blockers is somewhat uncertain, as a study with nisoldipine has shown an adverse effect in diabetic patients.[262] At present, calcium channel blockers are probably best used after ACE inhibitors, diuretics, and possibly beta blockers fail to achieve the target blood pressure.[254,255] Central alpha$_2$ agonists (e.g., clonidine), alpha$_1$ antagonists (e.g., prazosin, terazosin, and doxazosin), and combined alpha and beta antagonists (e.g., labetalol) also can be used, although orthostatic hypotension may limit their utility, particularly in patients with autonomic neuropathy.

DYSLIPIDEMIA

Severe hypertriglyceridemia may complicate DKA in type 1 diabetes mellitus, but it clears rapidly with insulin treatment. Serum triglyceride levels are usually elevated—sometimes strikingly so—in uncontrolled type 2 diabetes mellitus, and they are almost invariably accompanied by decreased HDL levels, an atherogenic combination. LDL levels are normal or slightly elevated; however, the LDL component may include a higher proportion of small, dense, more atherogenic particles. Restriction of saturated fat and calories, elimination of excess weight, exercise, and improved glycemic control reduce triglycerides and increase HDL.[262] When these measures are insufficient, gemfibrozil, fenofibrate, or benzafibrate should be prescribed with the purpose of decreasing triglycerides to less than 150 mg/dl and increasing HDL to greater than 35 mg/dl in men and greater than 45 mg/dl in women. For LDL levels greater than 100 mg/dl in patients with or without established coronary artery disease, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the drugs of choice. Simvastatin, pravastatin, and lovastatin have all been shown to decrease cardiovascular events in diabetic patients. Atorvastatin may have the greatest efficacy in lowering LDL and triglyceride levels. If necessary, tolerated doses of bile acid resins may be added. Niacin would be ideal monotherapy because it powerfully lowers triglyceride and LDL levels and increases HDL levels; however, its side effects often discourage compliance, and niacin can also increase blood glucose levels. An extended-release form of niacin, Niaspan, may be more acceptable and effective. If niacin is used as monotherapy or in combination with statins, the daily dosage should not exceed 3 g. Both niacin and statins require the monitoring of serum ALT levels.

MEASURES TO REDUCE RISK OF CARDIOVASCULAR DISEASE

Smoking

Referral to successful smoking-cessation programs and use of oral or dermal nicotine preparations during withdrawal from tobacco should be employed as needed to rid patients of this serious risk factor for cardiovascular disease. Success appears to be directly related to the amount of counseling and support provided by physicians or other professionals.[263]

Aspirin

In the Early Treatment of Diabetic Retinopathy Study, administration of 650 mg of aspirin a day resulted in a statistically significant 17% reduction in the risk of fatal plus nonfatal myocardial infarctions.[264] All-cause mortality and cardiovascular disease mortality tended to decrease, whereas strokes tended to increase, but none of these differences were statistically significant. Preventive use of aspirin is now recommended by the American Diabetes Association for patients who already have cardiovascular disease or who have other risk factors for cardiovascular disease.[265,266]

ACE Inhibitors

In the large, multicentered, randomized 5-year Heart Outcomes Prevention Evaluation (HOPE) trial,[267] ramipril in a single daily dose of 10 mg decreased major cardiovascular events, including myocardial infarction, stroke, heart failure, revascularization procedures, and death by 20% to 32% when compared with placebo. The 9,300 patients were at high risk at entry, and 38% had diabetes. All the diabetic patients benefited from ramipril therapy. Notably, many of the patients were normotensive at baseline, and the beneficial effect of the ACE inhibitor was not thought to be accounted for by the small decrease in average blood pressure. Patients with previous cardiovascular disease also benefited. The data indicated that treatment of 100 patients with ramipril for 4 years would prevent 15 events in seven patients.

Antioxidants

The HOPE study also compared the effect of 400 IU of vitamin E daily with that of placebo. Subjects received no benefit from vitamin E.[268] Although some observational and experimental studies have shown an association between antioxidants and protection from atherosclerosis, there are no firm data on which to base a recommendation for their routine use in diabetes.

MANAGEMENT OF SYMPTOMATIC CORONARY ARTERY DISEASE

Beta blockers, nitrates, and calcium channel blockers can all be used as in nondiabetic individuals, with the proviso that patients treated with insulin or beta cell stimulants should be cautioned about hypoglycemia. When a revascularization procedure has been deemed necessary, coronary artery bypass surgery has been reported to be superior to angioplasty in 5-year survival and recurrent myocardial infarction rates in patients receiving pharmacologic treatment for type 2 diabetes mellitus.[269] In patients without mandatory indications for immediate surgical intervention, such as significant left main coronary artery stenosis, a clinical research trial is currently attempting to determine whether a prompt revascularization procedure is superior to aggressive medical therapy. One study has shown that normalization of blood glucose levels with intravenous insulin during the first 3 days of an acute myocardial infarction, followed by intensive blood glucose control on an outpatient basis for at least 3 months, significantly decreased mortality for up to 3.5 years.[270] If intensive control of glycemia is used in patients with cardiovascular disease, prevention of hypoglycemia should especially be emphasized because, in rare instances, it may precipitate myocardial infarction or stroke.

Prevention and Treatment of Microvascular Complications

As noted above, intensive treatment of both type 1 and type 2 diabetes mellitus, aiming at normoglycemia, reduces the risks of development or progression of diabetic retinopathy, nephropathy, and neuropathy. The earlier such treatment is begun, the greater the benefit.[39] However, once these complications have reached stages of major clinical impact, their response to intensive glycemic control is unknown or at least unproved, with the possible exception of pancreas transplantation.[104] Fortunately,

there are forms of therapy for advanced complications that may ameliorate or prevent their worst manifestations.[271,272]

RETINOPATHY

Laser treatment of high-risk proliferative retinopathy and of macular edema has been demonstrated to preserve vision.[273] For proliferative retinopathy, panretinal scatter photocoagulation is performed to ablate ischemic retina in the periphery capable of producing VEGF. For macular edema, finely focused laser treatment is performed to close visibly leaking perimacular vessels that are demonstrated by fluorescein angiography. The role of the internist and ophthalmologist is to detect retinopathy requiring laser therapy before irreversible damage and loss of vision occur. Although fundus photography is the most sensitive means of detecting early retinopathy, ophthalmologists and even well-trained endocrinologists and internists can detect retinopathy by direct ophthalmoscopy.[274] An examination with the pupil dilated is preferable, but examination in a completely blackened room can be reasonably effective. In type 1 diabetes mellitus, significant retinopathy (beyond microaneurysms) seldom occurs before 5 years' duration, so that regular yearly ophthalmologic examinations do not need to commence until then. By contrast, 20% to 40% of patients with type 2 diabetes mellitus already have detectable retinopathy at the time of clinical onset and diagnosis.[275] Therefore, yearly ophthalmologic examinations should begin at the time of diagnosis. Pregnancy is a recognized risk factor for progression of retinopathy in type 1 diabetes mellitus,[276] and ophthalmologic examinations should be performed at the beginning of pregnancy and thereafter with a frequency dependent on the findings of the first examination. For patients with vitreous hemorrhage that does not clear or significant vitreous scarring and debris, vitrectomy can be performed. Fibroproliferative scars can be excised, and a detached retina can be reattached. The vitreous is replaced with a salt solution. In selected cases, these procedures can restore vision.

NEPHROPATHY

The best preventive approach for diabetic nephropathy in both type 1 and type 2 diabetes mellitus is to maintain a normal blood pressure.[257,277] In normotensive patients with type 1[278] and type 2[279] diabetes mellitus who develop microalbuminuria (30 to 300 mg/day), clinical trials have shown that ACE inhibitor or ARB treatment decreases the rate of progression from microalbuminuria to proteinuria to early renal insufficiency. Maintaining blood glucose near normal with intensive treatment also significantly reduces the risk of diabetic nephropathy.[32,37] If ESRD does develop, a renal transplant is the preferred replacement therapy; home peritoneal dialysis is superior to chronic hemodialysis because the latter is often complicated by vitreous hemorrhage, amputations, and septic episodes. With all forms of therapy for ESRD, mortality is higher in diabetic patients than nondiabetic patients largely because of cardiovascular complications.[280]

NEUROPATHY

Management of diabetic neuropathy is still largely symptomatic[271,272] and often inadequate. Gabapentin[281] in doses of up to 3 g/day has been added to the list of agents that include bedtime tricyclic antidepressants (e.g., nortriptyline), carbamazepine, and topical capsaicin for relief of pain and dysesthesias. Intensive blood glucose control may benefit patients with diabetic amyotrophy and radiculopathy. Prevention of foot ulcers remains very important; patient self-examination of the feet daily and physician-nurse examination at each office visit unequivocally reduce the risk of foot ulcer and amputation.[282] When a foot ulcer does occur, it should be treated aggressively with broad-spectrum antibiotics effective against staphylococci and anaerobes, vigorous debridement as necessary, radiographic examination for osteomyelitis, and sometimes special weight-bearing casts.[283] The use of locally applied growth factors appears promising to reduce healing time.[283] Aggravating effects of ischemia may be alleviated by revascularization of the leg when it is still possible to abort gangrene. Appropriate specialists should be consulted early for achievement of the best outcomes.

Management of autonomic neuropathy is especially challenging. Gastroparesis can benefit from frequent small feedings and either parenteral or liquid oral preparations of metoclopramide[284] or erythromycin.[285] Intermittent intubation to decompress a dilated full stomach may be required to relieve persistent vomiting or painful bloating. A feeding jejunostomy can be considered for intractable cases. Diarrhea sometimes responds to tetracycline antibiotics; clonidine and occasionally somatostatin are effective. Bladder dysfunction may be improved by oral bethanechol and regular timed voiding, but self-catheterization is necessary in severe cases of atony. Use of indwelling catheters should be minimized because of the danger of bacterial or fungal infection. Orthostatic hypotension is benefited by compression stockings, ample sodium intake, and fluorohydrocortisone. The use of midodrine is limited by the risks of excessive hypotension or urinary retention. Male impotence can be satisfactorily treated by penile injection or urethral insertion of alprostadil; by use of a simple vacuum pump; or, increasingly rarely, by implantation of a penile prosthesis. Sildenafil is effective for diabetic impotence,[286] but it may be dangerous in diabetic men with established or unsuspected coronary disease.

Diabetes Mellitus during Pregnancy

Women in their reproductive years with known diabetes of any type should be instructed to inform their physicians when they have decided to have a child. Conception when diabetes control is inadequate markedly increases the risk of major congenital abnormalities. This risk can be reduced to the nondiabetic background rate when control is excellent.[287,288] Therefore, the patient's HbA_{1c} should be brought as close to normal as possible before conception. One recent recommendation is that the average of preprandial and postprandial home blood glucose test results should be less than 126 mg/dl and HbA_{1c} should be brought to at least less than 7.0%.[288] The patients taking oral hypoglycemic agents should be switched to insulin and excellent control established before conception. Nondiabetic women should be screened for gestational diabetes mellitus (GDM) during weeks 24 to 28 of pregnancy by glucose loading.

Throughout pregnancy, normoglycemia (relative to the normal pregnant state) is required to prevent intrauterine death and perinatal morbidity and mortality. Preprandial blood glucose targets during pregnancy are 60 to 90 mg/dl and postprandial targets are less than 120 to 140 mg/dl.[289,290] Most patients with GDM detected by routine screening can be tried on diet treatment for 1 to 2 weeks. In obese women, either 1,500 kcal or 35 kcal/kg prepregnancy weight has been recommended.[287] In 15% to 20% of cases, persistence of FBG of at least 105 mg/dl or 2-hour postprandial values of at least 120 to 140 mg/dl mandates institution of insulin treatment. The blood glucose control targets can then often be achieved with injections of NPH plus regular insulin before breakfast, regular insulin before supper, and NPH

insulin at bedtime. Lispro insulin has not yet been approved for use during pregnancy. Pregnant women with type 1 diabetes mellitus need to continue intensive treatment as described previously. Pregnant women with type 2 diabetes mellitus often respond to insulin regimens as described for GDM. After delivery, insulin requirements disappear almost instantaneously in patients with GDM and may decrease strikingly from those of the third trimester in women with type 1 diabetes mellitus.

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References

1. American Diabetes Association: Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 23(suppl 1):S4, 2000

2. DECODE Study Group: Will new diagnostic criteria for diabetes mellitus change phenotype of patients with diabetes? Reanalysis of European epidemiological data. BMJ 317:371, 1998

3. Kjos SL, Buchanan TA: Gestational diabetes mellitus. Current Concepts 341:1749, 1999

4. Barnes AJ, Bloom SR, Goerge K, et al: Ketoacidosis in pancreatectomized man. N Engl J Med 296:1250, 1977

5. Hirsch IB, Paauw DS: Diabetes management in special situations. Curr Therap Diabetes 26:631, 1997

6. Gurwitz JH, Bohn RL, Glynn RJ, et al: Glucocorticoids and the risk for initiation of hypoglycemic therapy. Arch Intern Med 154:97, 1994

7. Matsumoto K, Yamasaki H, Akazawa S, et al: High-dose but not low-dose dexamethasone impairs glucose tolerance by inducing compensatory failure of pancreatic β-cells in normal men. J Clin Endocrinol Metab 81:2621, 1996

8. LaPorte RE, Matsushima M, Chang Y-F: Prevalence and incidence of insulin-dependent diabetes. Diabetes in America, 2nd ed. NIDDK NIH Publication No. 95-1468, 1995

9. Harris MI, Flegal KM, Cowie CC, et al: Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. Diabetes Care 21:518, 1998

10. Kenny SJ, Aubert RE, Geiss LS: Prevalence and incidence of non-insulin-dependent diabetes. Diabetes in America, 2nd ed. NIDDK NIH Publication No. 95-1468, 1995

11. King H, Aubert RE, Herman WH: Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414, 1998

12. Mokdad AH, Ford ES, Bowman BA, et al: Diabetes trends in the U.S.: 1990–1998. Diabetes Care 23:1278, 2000

13. Mokdad AH, Serdula MK, Dietz WH, et al: The spread of the obesity epidemic in the United States, 1991–1998. JAMA 282:1519, 1999

14. Harris MI: Health care and health status and outcomes for patients with type 2 diabetes. Diabetes Care 23:754, 2000

15. Harris MI, Eastman RC, Cowie CC, et al: Racial and ethnic differences in glycemic control of adults with type 2 diabetes. Diabetes Care 22:403, 1999

16. National Task Force on the Prevention and Treatment of Obesity: Overweight, obesity, and health risk. Arch Intern Med 160:898, 2000

17. Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: executive summary. Am J Clin Nutr 68:899, 1998

18. Ruderman N, Chisholm D, Pi-Sunyer X, et al: The metabolically obese, normal-weight individual revisited. Diabetes 47:699, 1998

19. Rewers M, Hamman RF: Risk factors for non-insulin-dependent diabetes. Diabetes in America, 2nd ed. NIDDK NIH Publication No. 95-1468, 1995

20. Genuth S: Hormones of the pancreatic islets. Physiology, 4th ed. Berne RM, Levy MN, Eds. Mosby, St. Louis, 1998, p 822

21. Davis MD: Diabetic retinopathy. Diabetes Care 15:1844, 1992

22. Goldfarb S: Diabetic nephropathy. Primer on Kidney Diseases. Greenberg A, Cheung AK, Falk RJ, et al, Eds. Academic Press, San Diego, 1994, p 112

23. Breyer JA: Diabetic nephropathy in insulin-dependent patients. Am J Kidney Dis 20:533, 1992

24. Ritz E, Stefanski A: Diabetic nephropathy in type II diabetes. Am J Kidney Dis 27:167, 1996

25. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 311:89, 1984

26. Andersen AR, Christiansen JS, Andersen JK, et al: Diabetic nephropathy in type 1 (insulin-dependent) diabetes: an epidemiological study. Diabetologia 25:496, 1983

27. Eaton S, Tesfaye S: Clinical manifestations and measurement of somatic neuropathy. Diabetes Reviews 7:312, 1999

28. Rith-Najarian SJ, Stolusky T, Gohdes DM: Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting: a prospective evaluation of simple screening criteria. Diabetes Care 15:1386, 1992

29. Malik RA: Pathology and pathogenesis of diabetic neuropathy. Diabetes Reviews 7:253, 1999

30. Krendel DA, Costigan DA, Hopkins LC: Successful treatment of neuropathies in patients with diabetes mellitus. Arch Neurol 52:1053, 1995

31. Genuth SM: The case for blood glucose control. Advances in Internal Medicine, Vol 40. Schrier RW, Abboud FM, Baxter JD, et al, Eds. Mosby, St. Louis, 1995, p 573

32. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 329:977, 1993

33. The Diabetes Control and Complications Trial Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 18:361, 1995

34. The Diabetes Control and Complications Trial Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. Diabetes Care 18:1415, 1995

35. The Diabetes Control and Complications Trial Research Group: Resource utilization and costs of care in the Diabetes Control and Complications Trial. Diabetes Care 18:1468, 1995

36. The Diabetes Control and Complications Trial Research Group: Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. JAMA 276:1409, 1996

37. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837, 1998

38. UK Prospective Diabetes Study (UKPDS) Group: Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854, 1998

39. The Diabetes Control and Complications Trial Research Group: The relationship of glycemic exposure (HbA_{1c}) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. Diabetes 44:968, 1995

40. Stratton IM, Adler AI, Neil HA, et al: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321:405, 2000

41. The Diabetes Control and Complications Trial Research Group: The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes 45:1289, 1996

42. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. JAMA 287:2563, 2002

43. Vlassara H, Bucala R, Striker L: Pathogenic effects of advanced glycosylation: biochemical, biologic, and clinical implications for diabetes and aging. Lab Invest 70:138, 1994

44. Brownlee M: Negative consequences of glycation. Metabolism 49(suppl 1):9, 2000

45. Monnier VM, Bautista O, Kenny D, et al: Skin collagen glycation, glycoxidation, and crosslinking are lower in subjects with long-term intensive versus conventional therapy of type 1 diabetes: relevance of glycated collagen products versus HbA_{1c} as markers of diabetic complications. Diabetes 48:870, 1999

46. Baynes JW, Thorpe SR: Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48:1, 1999

47. Carrington AL, Litchfield JE: The aldose reductase pathway and nonenzymatic glycation in the pathogenesis of diabetic neuropathy: a critical review for the end of the 20th century. Diabetes Reviews 7:275, 1999

48. Ishii H, Koya D, King GL: Protein kinase C activation and its role in the development of vascular complications in diabetes mellitus. J Mol Med 76:21, 1998

49. Brownlee M: Biochemistry and molecular cell biology of diabetic complications. Nature 414:813, 2001

50. Nishikawa T, Edelstein D, Du XL, et al: Normalizing mitochondrial superoxide production blocks three pathways of hyperglycaemic damage. Nature 404:787, 2000

51. Quinn M, Angelico MC, Warram JH, et al: Familial factors determine the development of diabetic nephropathy in patients with IDDM. Diabetologia 39:940, 1996

52. The Diabetes Control and Complications Trial Research Group: Clustering of long-term complications in families with diabetes in the Diabetes Control and Complications Trial. Diabetes 46:1829, 1997

53. Thai A-C, Eisenbarth GS: Natural history of IDDM. Diabetes Reviews 1:1, 1993

54. Foulis AK, Liddle CN, Farquharson MA, et al: The histopathology of the pancreas in type 1 (insulin-dependent) diabetes mellitus: a 25-year review of deaths in patients under 20 years of age in the United Kingdom. Diabetologia 29:267, 1986

55. Eisenbarth GS: Type 1 diabetes mellitus: a chronic autoimmune disease. N Engl J Med 314:1360, 1986

56. Faustman D, Eisenbarth G, Daley J, et al: Abnormal T-lymphocyte subsets in type 1 diabetes. Diabetes 38:1462, 1989

57. Rossini AA, Greiner DL, Friedman HP, et al: Immunopathogenesis of diabetes mellitus. Diabetes Reviews 1:43, 1993

58. Littorin B, Sundkvist G, Hagopian W, et al: Islet cell and glutamic acid decarboxylase antibodies present at diagnosis of diabetes predict the need for insulin treatment. Diabetes Care 22:409, 1999

59. Falorni A, Lernmark A: Humoral autoimmunity. Diabetes Mellitus: A Fundamental and Clinical Text, 1st ed. LeRoith D, Taylor SI, Olefsky JM, Eds. Lippincott-Raven Publishers, Philadelphia, 1996, p 298

60. Palmer JP, Asplin CM, Clemons P, et al: Insulin antibodies in insulin-dependent diabetics before insulin treatment. Science 222:1337, 1983

61. Feutren G, Papoz L, Assan R, et al: Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset: results of a multicentre double-blind trial. Lancet 2:119, 1986

62. Bougneres PF, Landais P, Boisson C, et al: Limited duration of remission of insulin dependency in children with recent overt type 1 diabetes treated with low-dose cy-

closporin. Diabetes 39:1264, 1990

63. Riley WJ, Maclaren NK, Krischer J, et al: A prospective study of the development of diabetes in relatives of patients with insulin-dependent diabetes. N Engl J Med 323:1167, 1990

64. Tarn AC, Thomas JM, Dean BM, et al: Predicting insulin-dependent diabetes. Lancet 1:845, 1988

65. Ziegler AG, Herskowitz RD, Jackson RA, et al: Predicting type 1 diabetes. Diabetes Care 13:762, 1990

66. Srikanta S, Ganda OP, Gleason RE, et al: Pre-type 1 diabetes: linear loss of beta cell response to intravenous glucose. Diabetes 33:717, 1984

67. Rayfield EJ, Ishimura K: Environmental factors and insulin-dependent diabetes mellitus. Diabetes Metab Rev 3:925, 1987

68. Jones DB, Armstrong NW: Coxsackie virus and diabetes revisited. Nat Med 1:284, 1995

69. Agner T, Damm P, Binder C: Remission in IDDM: prospective study of basal C-peptide and insulin dose in 268 consecutive patients. Diabetes Care 10:164, 1987

70. Heinze E, Beischer W, Keller L, et al: C-peptide secretion during the remission phase of juvenile diabetes. Diabetes 27:670, 1978

71. Shah SC, Malone JI, Simpson NE: A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. N Engl J Med 320:550, 1989

72. The Diabetes Control and Complications Trial Research Group: Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual beta-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). J Clin Endocrinol Metab 65:30, 1987

73. Gorsuch AN, Spencer KM, Lister J, et al: Evidence for a long prediabetic period in type I (insulin-dependent) diabetes mellitus. Lancet 2:1363, 1981

74. Karjalainen J, Salmela P, Ilonen J, et al: A comparison of childhood and adult type I diabetes mellitus. N Engl J Med 320:881, 1989

75. Pugliese A: Unraveling the genetics of insulin-dependent type 1A diabetes: the search must go on. Diabetes Reviews 7:39, 1999

76. Baisch JM, Weeks T, Giles R, et al: Analysis of HLA-DQ genotypes and susceptibility in insulin-dependent diabetes mellitus. N Engl J Med 322:1836, 1990

77. Nepom GT: Immunogenetics and IDDM. Diabetes Reviews 1:93, 1993

78. Palmer JP: Predicting IDDM: use of humoral immune markers. Diabetes Reviews 1:104, 1993

79. Genuth SM: Plasma insulin and glucose profiles in normal, obese, and diabetic persons. Ann Intern Med 79:812, 1973

80. Nair KS, Halliday D, Garrow JS: Increased energy expenditure in poorly controlled type I (insulin-dependent) diabetic patients. Diabetologia 27:13, 1984

81. American Diabetes Association: Standards of medical care for patients with diabetes mellitus. Diabetes Care 24:533, 2001

82. The DCCT Research Group: Diabetes Control and Complications Trial (DCCT): results of feasibility study. Diabetes Care 10:1, 1987

83. Goldstein DE, Little RR, Lorenz RA, et al: Tests of glycemia in diabetes. Diabetes Care 18:896, 1995

84. Larsen ML, Horder M, Mogensen EF: Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus. N Engl J Med 323:1021, 1990

85. American Diabetes Association: Tests of glycemia in diabetes. Diabetes Care 23(suppl 1):S80, 2000

86. Cagliero E, Levina EV, Nathan DM: Immediate feedback of HbA_{1c} levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. Diabetes Care 22:1785, 1999

87. Skyler JS: Insulin treatment. Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. Lebovitz HE, Ed. American Diabetes Association, Alexandria, Virginia, 1998, p 186

88. Hirsch IB: Type 1 diabetes mellitus and the use of flexible insulin regimens. Am Fam Physician 60:2343, 1999

89. Lee WL, Zinman B: From insulin to insulin analogs: progress in the treatment of type 1 diabetes. Diabetes Reviews 6:73, 1998

90. Garg SK, Carmain JA, Braddy KC, et al: Pre-meal insulin analogue insulin lispro vs Humulin® R insulin treatment in young subjects with type 1 diabetes. Diabet Med 13:47, 1996

91. Anderson JH Jr, Brunelle RL, Koivisto VA, et al: Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes 46:265, 1997

92. Del Sindaco P, Ciofetta M, Lalli C, et al: Use of the short-acting insulin analogue lispro in intensive treatment of type 1 diabetes mellitus: importance of appropriate replacement of basal insulin and time-interval injection-meal. Diabet Med 15:592, 1998

93. Raskin P, Guthrie RA, Leiter L, et al: Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care 23:583, 2000

94. Heinemann L, Linkeschova R, Rave K, et al: Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. Diabetes Care 23:644, 2000

95. Rosenstock J, Park G, Zimmerman J: Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. Diabetes Care 23:1137, 2000

96. Ratner RE, Hirsch IB, Neifing JL, et al: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. Diabetes Care 23:639, 2000

97. Mecklenburg RS: Insulin-pump therapy. Therapy for Diabetes Mellitus and Related Disorders, 3rd ed. Lebovitz HE, Ed. American Diabetes Association, Alexandria, Virginia, 1998, p 204

98. Diabetes Control and Complications Trial Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care 18:361, 1995

99. Dunn FL, Nathan DM, Scavini M, et al: Long-term therapy of IDDM with an implantable insulin pump. Diabetes Care 20:59, 1997

100. Salzman R, Manson JE, Griffing GT, et al: Intranasal aerolized insulin: mixed-meal studies and long-term use in type I diabetes. N Engl J Med 312:1078, 1985

101. Jendle JH, Karlberg BE: Effects of intrapulmonary insulin in patients with non-insulin-dependent diabetes. Scand J Clin Lab Invest 56:555, 1996

102. Selam JL: Inhaled insulin for the treatment of diabetes: projects and devices. Expert Opin Pharmacother 4:1373, 2003

103. Robertson RP, Holohan TV, Genuth S: Therapeutic controversy: pancreas transplantation for type I diabetes. J Clin Endocrinol Metab 83:1868, 1998

104. Robertson RP, Davis C, Larsen J, et al: Pancreas and islet transplantation for patients with diabetes. Diabetes Care 23:112, 2000

105. Shapiro J, Lakey JRT, Ryan EA, et al: Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 343:230, 2000

106. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care 23:543, 2000

107. Jenkins DJ, Wolever TM, Taylor RH, et al: Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 34:362, 1981

108. Franz MJ, Horton ES, Bantle JP, et al: Nutrition principles for the management of diabetes and related complications. Diabetes Care 17:490, 1994

109. American Diabetes Association: Diabetes mellitus and exercise. Diabetes Care 23(suppl 1):S50, 2000

110. Genuth SM: Diabetic ketoacidosis and hyperglycemic hyperosmolar coma. Current Therapy in Endocrinology and Metabolism, 6th ed. Bardin CW, Ed. Mosby–Year Book, St. Louis, 1997, p 438

111. Foster DW, McGarry JD: The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 309:159, 1983

112. Barrett EJ, DeFronzo RA, Bevilacqua S, et al: Insulin resistance in diabetic ketoacidosis. Diabetes 31:923, 1982

113. Burge MR, Hardy KJ, Schade DS: Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. J Clin Endocrinol Metab 76:1192, 1993

114. DeFronzo RA, Matsuda M, Barrett EJ: Diabetic ketoacidosis: a combined metabolic-nephrologic approach to therapy. Diabetes Reviews 2:209, 1994

115. Kitabchi AE, Wall BM: Diabetic ketoacidosis. Med Clin North Am 79:9, 1995

116. Waldhausl W, Kleinberger G, Korn A, et al: Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. Diabetes 28:577, 1979

117. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. Am J Med 90:450, 1991

118. Gale EA, Tattersall RB: Unrecognised nocturnal hypoglycaemia in insulin-treated diabetics. Lancet 1:1049, 1979

119. Cryer PE: Hypoglycemia: the limiting factor in the management of IDDM. Diabetes 43:1378, 1994

120. Heller SR, Macdonald IA, Herbert M, et al: Influence of sympathetic nervous system on hypoglycaemic warning symptoms. Lancet 2:359, 1987

121. Mokan M, Mitrakou A, Veneman T, et al: Hypoglycemia unawareness in IDDM. Diabetes Care 17:1397, 1994

122. Dagogo-Jack S, Rattarasarn C, Cryer PE: Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. Diabetes 43:1426, 1994

123. Fanelli C, Pampanelli S, Epifano L, et al: Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia 37:1265, 1994

124. Boyle PJ, Kempers SF, O'Connor AM, et al: Brain glucose uptake and unawareness of hypoglycemia in patients with insulin-dependent diabetes mellitus. N Engl J Med 333:1726, 1995

125. Wahren J, Ekberg K, Fernqvist-Forbes E, et al: Brain substrate utilisation during acute hypoglycaemia. Diabetologia 42:812, 1999

126. The Diabetes Control and Complications Trial Research Group: Effects of intensive diabetes therapy on neuropsychological function in adults in the Diabetes Control and Complications Trial. Ann Intern Med 124:379, 1996

127. Kramer L, Fasching P, Madl C, et al: Previous episodes of hypoglycemic coma are not associated with permanent cognitive brain dysfunction in IDDM patients on intensive insulin treatment. Diabetes 47:1909, 1998

128. Boden G: Pathogenesis of type 2 diabetes: insulin resistance. Endocrinol Metab Clin North Am 30:801, 2001

129. Haffner SM, D'Agostino R, Mykkänen L, et al: Insulin sensitivity in subjects with type 2 diabetes. Diabetes Care 22:562, 1999

130. Haffner SM, Stern MP, Hazuda HP, et al: Increased insulin concentrations in nondiabetic offspring of diabetic parents. N Engl J Med 319:1297, 1988

131. Lillioja S, Mott DM, Howard BV, et al: Impaired glucose tolerance as a disorder of insulin action: longitudinal and cross-sectional studies in Pima Indians. N Engl J Med 318:1217, 1988

132. Saad MF, Knowler WC, Pettitt DJ, et al: Sequential changes in serum insulin concentration during development of non-insulin-dependent diabetes. Lancet 1:1356, 1989

133. Warram JH, Martin BC, Krolewski AS, et al: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic patients. Ann Intern Med 113:909, 1990

134. O'Meara NM, Sturis J, Van Cauter E, et al: Lack of control by glucose of ultradian insulin secretory oscillations in impaired glucose tolerance and in non-insulin-dependent diabetes mellitus. J Clin Invest 92:262, 1993

135. Porte D Jr: Beta-cells in type II diabetes mellitus. Diabetes 40:166, 1991

136. Hollingdal M, Juhl CB, Pincus SM, et al: Failure of physiological plasma glucose excursions to entrain high-frequency pulsatile insulin secretion in type 2 diabetes. Diabetes 49:1334, 2000

137. Polonsky KS: Evolution of beta-cell dysfunction in impaired glucose tolerance and diabetes. Exp Clin Endocrinol Diabetes 107(suppl 4):S124, 1999

138. Pimenta W, Korytkowski M, Mitrakou A, et al: Pancreatic beta-cell dysfunction as the primary genetic lesion in NIDDM: evidence from studies in normal glucose-tolerant individuals with a first-degree NIDDM relative. JAMA 273:1855, 1995

139. Cavaghan MK, Ehrmann DA, Polonsky KS: Interactions between insulin resistance and insulin secretion in the development of glucose intolerance. J Clin Invest 106:329, 2000

140. Rossetti L, Giaccari A, DeFronzo RA: Glucose toxicity. Diabetes Care 13:610, 1990

141. Cohen M, Crosbie C, Cusworth L, et al: Insulin—not always a life sentence: withdrawal of insulin therapy in non-insulin-dependent diabetes. Diabetes Res 1:31, 1984

142. Saltiel AR: The molecular and physiological basis of insulin resistance: emerging implications for metabolic and cardiovascular diseases. J Clin Invest 106:163, 2000

143. Stern MP: Strategies and prospects for finding insulin resistance genes. J Clin Invest 106:323, 2000

144. Del Prato S, Bonadonna RC, Bonora E, et al: Characterization of cellular defects of insulin action in type 2 (non-insulin-dependent) diabetes mellitus. J Clin Invest 91:484, 1993

145. Pessin JE, Saltiel AR: Signaling pathways in insulin action: molecular targets of insulin resistance. J Clin Invest 106:165, 2000

146. Reaven GM, Chen YD: Role of abnormal free fatty acid metabolism in the development of non-insulin-dependent diabetes mellitus. Am J Med 85:106, 1988

147. Shulman GI: Cellular mechanisms of insulin resistance. J Clin Invest 106:171, 2000

148. Røder ME, Porter D Jr, Schwartz RS, et al: Disproportionately elevated proinsulin levels reflect the degree of impaired B cell secretory capacity in patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 83:604, 1998

149. Rachman J, Levy JC, Barrow BA, et al: Relative hyperproinsulinemia of NIDDM persists despite the reduction of hyperglycemia with insulin or sulfonylurea therapy. Diabetes 46:1557, 1997

150. Genuth SM: Hormones of the pancreatic islets. Physiology, 4th ed. Berne RM, Levy MN, Eds. Mosby, St. Louis, 1998, p 822

151. Brunzell JD, Robertson RP, Lerner RL, et al: Relationships between fasting plasma glucose levels and insulin secretion during intravenous glucose tolerance tests. J Clin Endocrinol Metab 42:222, 1976

152. Kahn SE, Andrikopoulos S, Verchere CB: Islet amyloid: a long-recognized but underappreciated pathological feature of type 2 diabetes. Diabetes 48:241, 1999

153. Groop LC, Bottazzo GF, Doniach D: Islet cell antibodies identify latent type 1 diabetes in patients aged 35-75 years at diagnosis. Diabetes 35:237, 1986

154. Turner R, Stratton I, Horton V, et al: UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. Lancet 351:1288, 1997

155. Torn C, Landin-Olsson M, Ostman J, et al: Glutamic acid decarboxylase antibodies (GADA) is the most important factor for prediction of insulin therapy within 3 years in young adult diabetic patients not classified as type 1 diabetes on clinical grounds. Diabetes Metab Res Rev 16:442, 2000

156. Executive Summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA 285:2486, 2001

157. Alberti KG, Zimmet PZ: Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus: provisional report of a WHO consultation. Diabetic Med 15:539, 1998

158. Kahn BB, Flier JS: Obesity and insulin resistance. J Clin Invest 106:473, 2000

159. Gastaldelli A, Baldi S, Pettiti M, et al: Influence of obesity and type 2 diabetes on gluconeogenesis and glucose output in humans. Diabetes 49:1367, 2000

160. Colditz GA, Willett WC, Rotnitzky A, et al: Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 122:481, 1995

161. Long SD, O'Brien K, MacDonald KG Jr, et al: Weight loss in severely obese subjects prevents the progression of impaired glucose tolerance to type II diabetes: a longitudinal interventional study. Diabetes Care 17:372, 1994

162. Montague CT, O'Rahilly S: The perils of portliness: causes and consequences of visceral adiposity. Diabetes 49:883, 2000

163. Ford ES, Giles WH, Dietz WH: Prevalence of the metabolic syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 287:356, 2002

164. Alexander CM, Landsman PB, Teutsch SM, et al: NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 52:1210, 2003

165. The Diabetes Prevention Program Research Group: The Diabetes Prevention Program: design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care 22:623, 1999

166. Tattersall RB, Pyke DA: Diabetes in identical twins. Lancet 2:1120, 1972

167. Stern MP: Strategies and prospects for finding insulin resistance genes. J Clin Invest 106:323, 2000

168. Habener JF, Stoffers DA: A newly discovered role of transcription factors involved in pancreas development and the pathogenesis of diabetes mellitus. Proc Assoc Am Physicians 110:12, 1998

169. Froguel P, Zouali H, Vionnet N, et al: Familial hyperglycemia due to mutations in glucokinase: definition of a subtype of diabetes mellitus. N Engl J Med 328:697, 1993

170. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. N Engl J Med 346:393, 2002

171. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. Finnish Diabetes Prevention Study Group. N Engl J Med 344:1343, 2001

172. Pan X-R, Li G-W, Hu Y-H, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and diabetes study. Diabetes Care 20:537, 1997

173. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomized trial. STOP-NIDDM Trial Research Group. Lancet 359:2072, 2002

174. Buchanan TA, Xiang AH, Peters RK, et al: Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 51:2796, 2002

175. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM Trial. STOP-NIDDM Trial Research Group. JAMA 290:486, 2003

176. Bosello O, Armellini F, Zamboni M, et al: The benefits of modest weight loss in type II diabetes. Int J Obes Relat Metab Disord 21(suppl 1):S10, 1997

177. American Diabetes Association: Nutrition recommendations and principles for people with diabetes mellitus. Diabetes Care 24(suppl 1):S44, 2001

178. Chandalia M, Garg A, Lutjohann D, et al: Beneficial effects of high dietary fiber intake in patients with type 2 diabetes mellitus. N Engl J Med 342:1392, 2000

179. The National Task Force on the Prevention and Treatment of Obesity: Very low-calorie diets. JAMA 270:967, 1993

180. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study (UKPDS): VIII: study design, progress and performance. Diabetologia 34:877, 1991

181. UKPDS Group: UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. Metabolism 39:905, 1990

182. Kelley DE, Jneidi M: Orlistat in the treatment of type 2 diabetes mellitus. Expert Opin Pharmacother 3:599, 2002

183. Porte D Jr, Seeley RJ, Woods SC, et al: Obesity, diabetes and the central nervous system. Diabetologia 41:863, 1998

184. MacDonald KG, Long SD, Swanson MS, et al: The gastric bypass operation reduces the progression and mortality of non-insulin-dependent diabetes mellitus. J Gastrointest Surg 1:213, 1997

185. O'Brien PE, Brown WA, Smith A, et al: Prospective study of a laparoscopically placed, adjustable gastric band in the treatment of morbid obesity. Br J Surg 85:113, 1999

186. Zinman B, Ruderman N, Campaigne BN, et al: Physical activity/exercise and diabetes mellitus. Diabetes Care 26(suppl 1):S73, 2003

187. Wei M, Gibbons LW, Kampert JB, et al: Low cardiorespiratory fitness and physical inactivity as predictors of mortality in men with type 2 diabetes. Ann Intern Med 132:605, 2000

188. Turner RC, Cull CA, Frighi V, et al: Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus. JAMA 281:2005, 1999

189. Riddle M: The 2 defects of type 2 diabetes: combining drugs to treat both insulin deficiency and insulin resistance. Am J Med 108(suppl 6a):S1, 2000

190. Ashcroft FM: Mechanisms of the Glycaemic Effects of Sulfonylureas. Horm Metab Res 28:456, 1996

191. Shorr RI, Ray WA, Daugherty JR, et al: Individual sulfonylureas and serious hypoglycemia in older people. J Am Geriatr Soc 44:751, 1996

192. Shorr RI, Ray WA, Daugherty JR, et al: Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med 157:1681, 1997

193. University Group Diabetes Program: A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. I: Design, methods and baseline results. II: Mortality results. Diabetes 19:747, 1970

194. Brady PA, Terzic A: The sulfonylurea controversy: more questions from the heart. J Am Coll Cardiol 31:950, 1998

195. Schade DS, Jovanovic L, Schneider J: A placebo-controlled, randomized study of glimepiride in patients with type 2 diabetes mellitus for whom diet therapy is unsuccessful. J Clin Pharmacol 38:636, 1998

196. Lebovitz HE: Insulin secretagogues: old and new. Diabetes Reviews 7:139, 1999

197. Fuhlendorff J, Rorsman P, Kofod H, et al: Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. Diabetes 47:345, 1998

198. Lebovitz HE: Alpha-glucosidase inhibitors. Current Therapies for Diabetes 26:539, 1997

199. Coniff RF, Shapiro JA, Robbins D, et al: Reduction of glycosylated hemoglobin and postprandial hyperglycemia by acarbose in patients with NIDDM: a placebo-controlled dose-comparison study. Diabetes Care 18:817, 1995

200. Kirpichnikov D, McFarlane SI, Sowers JR: Metformin: an update. Ann Intern Med 137:25, 2002

201. Stumvoll N, Nurjhan N, Perriello G, et al: Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 333:550, 1995

202. Inzucchi SE, Maggs DG, Spollett GR, et al: Efficacy and metabolic effects of metformin and troglitazone in type II diabetes mellitus. N Engl J Med 338:867, 1998

203. Multicenter Metformin Study Group: Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 333:541, 1995

204. Lebovitz HE: Effects of oral antihyperglycemic agents in modifying macrovascular risk factors in type 2 diabetes. Diabetes Care 22(suppl 3):S41, 1999

205. Garber AJ, Duncan TG, Goodman AM, et al: Efficacy of metformin in type II diabetes: results of a double-blind, placebo-controlled, dose-response trial. Am J Med 102:491, 1997

206. Lalau JD, Lacroix C, Compagnon P, et al: Role of metformin accumulation in metformin-associated lactic acidosis. Diabetes Care 18:779, 1995

207. Lalau JD, Westeel PF, Debussche X, et al: Bicarbonate haemodialysis: an adequate treatment for lactic acidosis in diabetics treated by metformin. Intensive Care Med 13:383, 1987

208. Henry RR: Thiazolidinediones. Current Therapies for Diabetes 26:553, 1997

209. Maggs DG, Buchanan TA, Burant CF, et al: Metabolic effects of troglitazone monotherapy in type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 128:176, 1998

210. Olefsky JM: Treatment of insulin resistance with peroxisome proliferator-activated receptor γ agonists. J Clin Invest 106:467, 2000

211. Akazawa S, Sun F, Ito M, et al: Efficacy of troglitazone on body fat distribution in type 2 diabetes. Diabetes Care 23:1067, 2000

212. Minamikawa J, Tanaka S, Yamauchi M, et al: Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. J Clin Endocrinol Metab 83:1818, 1998

213. Kato K, Satoh H, Endo Y, et al: Thiazolidinediones down-regulate plasminogen activator inhibitor type 1 expression in human vascular endothelial cells: a possible role for PPARgamma in endothelial function. Biochem Biophys Res Commun 258:431, 1999

214. Yamakawa K, Hosoi M, Fukumoto S, et al: Pioglitazone inhibits plasminogen activator inhibitor–1 expression in human vascular smooth muscle cell (abstr). Diabetes 47:A366, 1998

215. Murakami T, Mizuno S, Ohsato K, et al: Effects of troglitazone on frequency of coronary vasospastic-induced angina pectoris in patients with diabetes mellitus. Am J Cardiol 84:92, 1999

216. Avena R, Mitchell ME, Nylen ES, et al: Insulin action enhancement normalizes brachial artery vasoactivity in patients with peripheral vascular disease and occult diabetes. J Vasc Surg 28:1024, 1998

217. Kotchen TA, Zhang HY, Reddy S, et al: Effect of pioglitazone on vascular reactivity in vivo and in vitro. Am J Physiol 270:R660, 1996

218. Takagi T, Yoshida K, Akasaka T, et al: Troglitazone reduces intimal hyperplasia after coronary stent implantation in patients with type 2 diabetes mellitus: a serial intravascular ultrasound study (abstr). J Am Coll Cardiol 33(suppl A):100A, 1999

219. Tack CJJ, Smits P, Demacker PNM, et al: Troglitazone decreases the proportion of small, dense LDL and increases the resistance of LDL to oxidation in obese subjects. Diabetes Care 21:796, 1998

220. Winter WE, Maclaren NK, Riley WJ, et al: Maturity-onset diabetes of youth in black Americans. N Engl J Med 316:285, 1987

221. Banerji MA, Lebovitz HE: Insulin-sensitive and insulin-resistant variants in NIDDM. Diabetes 38:784, 1989

222. Genuth S: Insulin in non–insulin-dependent patients. Adv Endocrinol Metab 3:89, 1992

223. Riddle MC: Evening insulin strategy. Diabetes Care 13:676, 1990

224. Yki-Jarvinen H, Kauppila M, Kujansuu E, et al: Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 327:1426, 1992

225. Genuth SM, Martin P: Control of hyperglycemia in adult diabetics by pulsed insulin delivery. Diabetes 26:571, 1977

226. Henry RR, Gumbiner B, Ditzler T, et al: Intensive conventional insulin therapy for type II diabetes. Diabetes Care 16:21, 1993

227. Elliott TG, Viberti G: Relationship between insulin resistance and coronary heart disease in diabetes mellitus and the general population: a critical appraisal. Baillieres Clin Endocrinol Metab 7:1079, 1993

228. Genuth S: Exogenous insulin administration and cardiovascular risk in non–insulin-dependent and insulin-dependent diabetes mellitus. Ann Intern Med 124:104, 1996

229. Abraira C, Colwell JA, Nuttall FQ, et al: Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type II Diabetes (VA CSDM): results of the feasibility study. Diabetes Care 18:1113, 1995

230. Giugliano D, Quatraro A, Consoli G, et al: Metformin for obese, insulin-treated diabetic patients: improvement in glycaemic control and reduction of metabolic risk factors. Eur J Clin Pharmacol 44:107, 1993

231. Moses R, Slobodniuk R, Boyages S, et al: Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care 22:119, 1999

232. Horton ES, Whitehouse F, Ghazzi MN, et al: Troglitazone in combination with sulfonylurea restores glycemic control in patients with type 2 diabetes. Diabetes Care 21:1462, 1998

233. Raskin P, Jovanovic L, Berger S, et al: Repaglinide/troglitazone combination therapy: improved glycemic control in type 2 diabetes. Diabetes Care 23:979, 2000

234. U.K. Prospective Diabetes Study Group: U.K. Prospective Diabetes Study 16 – overview of 6 years' therapy of type II diabetes: a progressive disease. Diabetes 44:1249, 1995

235. Casner PR: Insulin-glyburide combination therapy for non-insulin-dependent diabetes mellitus: a long-term double blind, placebo-controlled trial. Clin Pharmacol Ther 44:594, 1988

236. Cruz-Caudillo JC, Sabatini S: Diabetic hyperosmolar syndrome. Nephron 69:201, 1995

237. Lorber D: Nonketotic hypertonicity in diabetes mellitus. Med Clin North Am 79:39, 1995

238. Stamler J, Vaccaro O, Neaton JD, et al: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 16:434, 1993

239. Barrett-Connor EL, Cohn BA, Wingard DL, et al: Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. JAMA 265:627, 1991

240. Haffner SM, Lehto S, Rönnemaa T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 339:229, 1998

241. Singer DE, Moulton AW, Nathan DM: Diabetic myocardial infarction: Interaction of diabetes with other preinfarction risk factors. Diabetes 38:350, 1989

242. Jensen T, Borch-Johnsen K, Kofoed-Enevoldsen A, et al: Coronary heart disease in young type 1 (insulin-dependent) diabetic patients with and without diabetic nephropathy: incidence and risk factors. Diabetologia 30:144, 1987

243. Grundy SM, Benjamin IJ, Burke GL, et al: Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 100:1134, 1999

244. Gu K, Cowie CC, Harris MI: Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971–1993. Diabetes Care 21:1138, 1998

245. Gu K, Cowie CC, Harris MI: Diabetes and decline in heart disease mortality in US adults. JAMA 281:1291, 1999

246. Moss SE, Klein R, Klein BEK, et al: The association of glycemia and cause-specific mortality in a diabetic population. Arch Intern Med 154:2473, 1994

247. Kuusisto J, Mykkänen L, Pyörälä K, et al: NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 43:960, 1994

248. Andersson DKG, Svärdsudd K: Long-term glycemic control relates to mortality in type II diabetes. Diabetes Care 18:1534, 1995

249. Wei M, Gaskill SP, Haffner SM, et al: Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality: the San Antonio Heart Study. Diabetes Care 21:1167, 1998

250. Stratton IM, Adler AI, Neil HAW, et al: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 321:405, 2000

251. UK Prospective Diabetes Study Group: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ 317:703, 1998

252. Nielson FS, Rossing P, Gall MA, et al: Long-term effect of lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy. Diabetes 46:1182, 1997

253. American Diabetes Association: Diabetic nephropathy. Diabetes Care 23:569, 2000

254. Pahor M, Psaty BM, Alderman MH, et al: Therapeutic benefits of ACE inhibitors and other antihypertensive drugs in patients with type 2 diabetes. Diabetes Care 23:888, 2000

255. Barkis GL, Williams M, Dworkin L, et al: Preserving renal function in adults with hypertension with diabetes: a consensus approach. Am J Kidney Dis 36:646, 2000

256. Effects of losartan on renal and cardiovascular outcome in patients with type 2 diabetes and nephropathy. RENAAL Study Investigators. N Engl J Med 345:861, 2001

257. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. N Engl J Med 345:870, 2001

258. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. Collaborative Study Group. N Engl J Med 345:851, 2001

259. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol. LIFE Study Group. Lancet 359:1004, 2002

260. UK Prospective Diabetes Study Group: Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. BMJ 317:713, 1998

261. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). ALLHAT Collaborative Research Group. JAMA 288:2981, 2002

262. Estacio RO, Jeffers BW, Hiatt WR, et al: The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. N Engl J Med 338:645, 1998

263. Haire-Joshu D, Glasgow RE, Tibbs TL: Smoking and diabetes. Diabetes Care 22:1887, 1999

264. ETDRS Investigators: Aspirin effects on mortality and morbidity in patients with diabetes mellitus: Early Treatment Diabetic Retinopathy Study report 14. JAMA 268:1292, 1992

265. American Diabetes Association: Aspirin therapy in diabetes. Diabetes Care 24(suppl 1):S62, 2001

266. Colwell JA: Aspirin therapy in diabetes. Diabetes Care 20:1767, 1997

267. The Heart Outcomes Prevention Evaluation Study Investigators: Effects of an angiotensin-converting–enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med 342:145, 2000

268. The Heart Outcomes Prevention Evaluation Study Investigators: Vitamin E supplementation and cardiovascular events in high-risk patients. N Engl J Med 342:154, 2000

269. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators: Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. N Engl J Med 335:217, 1996

270. Malmberg K, for the DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group: Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. BMJ 314:1512, 1997

271. Nathan DM: Long-term complications of diabetes mellitus. N Engl J Med 328:1676, 1993

272. Clark CM Jr, Lee DA: Prevention and treatment of the complications of diabetes mellitus. N Engl J Med 332:1210, 1995

273. Ferris FL III, Davis MD, Aiello LM: Treatment of diabetic retinopathy. Drug Therapy 341:667, 1999

274. Nathan DM, Fogel HA, Godine JE, et al: Role of diabetologist in evaluating diabetic retinopathy. Diabetes Care 14:26, 1991

275. Harris MI, Klein R, Welborn TA, et al: Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 15:815, 1992

276. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes Care 23:1084, 2000

277. Cooper ME: Pathogenesis, prevention, and treatment of diabetic nephropathy. Lancet 352:213, 1998

278. Lewis EJ, Hunsicker LG, Bain RP, et al: The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. N Engl J Med 329:1456, 1993

279. Ravid M, Savin H, Jutrin I, et al: Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 118:577, 1993

280. Foley RN, Culleton BF, Parfrey PS, et al: Cardiac disease in diabetic end-stage renal disease. Diabetologia 40:1307, 1997

281. Backonja M, Beydoun A, Edwards KR, et al: Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus. JAMA 280:1831, 1998

282. Litzelman DK, Slemenda CW, Langefeld CD, et al: Reduction of lower extremity clinical abnormalities in patients with non–insulin-dependent diabetes mellitus. Ann Intern Med 119:36, 1993

283. Mason J, O'Keeffe C, Hutchinson A, et al: A systematic review of foot ulcer in patients with type 2 diabetes mellitus. II: Treatment. Diabetic Medicine 16:889, 1999

284. McCallum RW, Ricci DA, Rakatansky H, et al: A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care 6:463, 1983

285. Janssens J, Peeters TL, Vantrappen G, et al: Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. N Engl J Med 322:1028, 1990

286. Sildenafil Diabetes Study Group: Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. JAMA 281:421, 1999

287. Kühl C: New approaches for the treatment of pregnant diabetic women. Diabetes Reviews 3:621, 1995

288. Langer O: Is normoglycemia the correct threshold to prevent complications in the pregnant diabetic patient? Diabetes Reviews 4:2, 1996

289. de Veciana M, Major CA, Morgan MA, et al: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med 333:1237, 1995

290. Kjos SL, Buchanan TA: Gestational diabetes mellitus. N Engl J Med 341:1749, 1999

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Figures 1, 4, 14, and 15 Seward Hung.