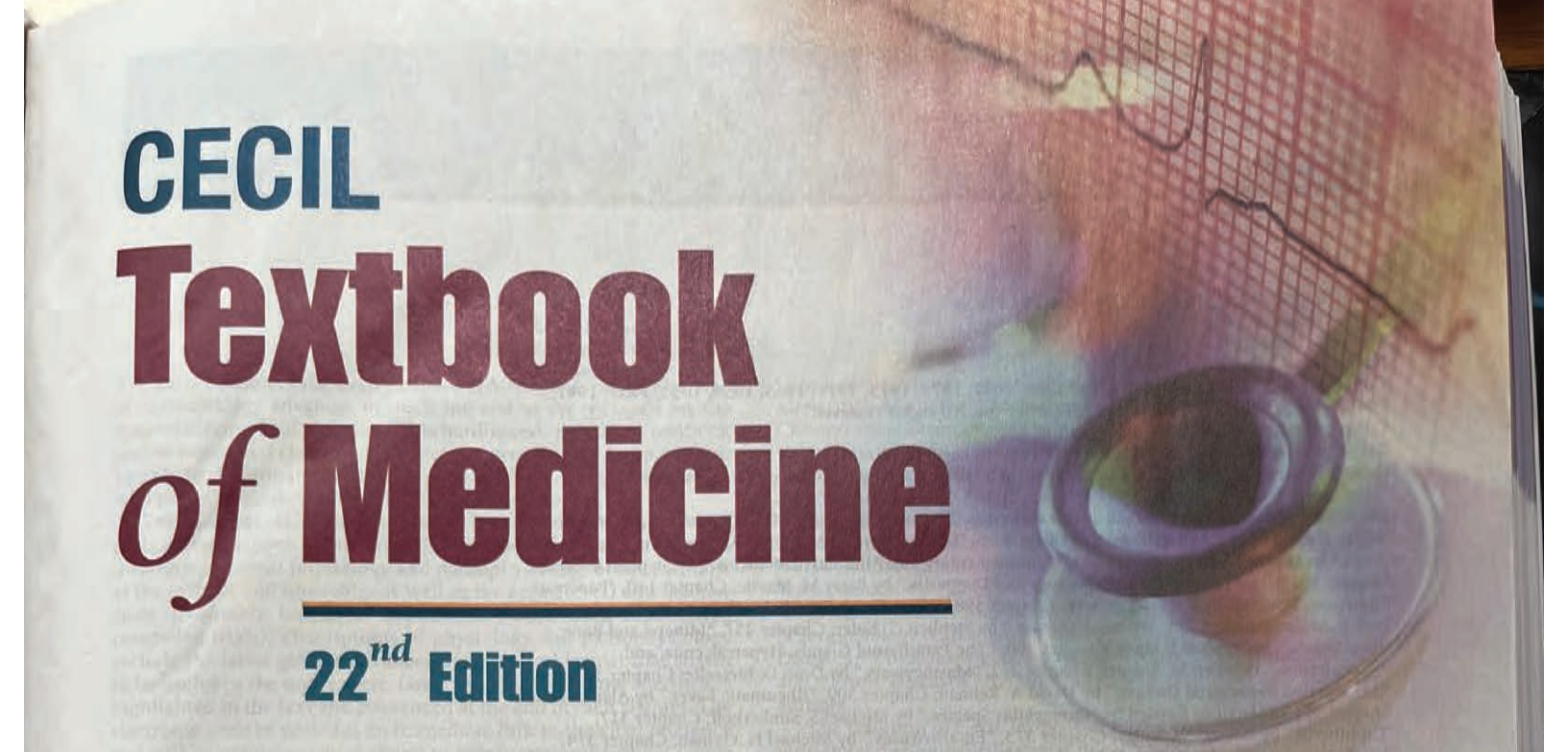

CECIL Textbook of Medicine

22nd Edition

VOLUME 2

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The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

CECIL TEXTBOOK OF MEDICINE, 22ND EDITION 0-7216-9652-X
Single Volume 0-7216-9653-8
Set (Vols. 1 and 2) 0-8089-2292-0
International Edition

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The Publisher

Library of Congress Cataloging-in-Publication Data

Cecil textbook of medicine / edited by Lee Goldman, Dennis Ausiello.—22nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-7216-9652-X
1. Internal medicine. I. Title: Textbook of medicine. II. Cecil, Russell L. (Russell La Fayette), 1881–1965. III. Goldman, Lee, MD. IV. Ausiello, D. A.
[DNLM: 1. Medicine. WB 100 C3888 2004]
RC46.C423 2004
616–dc21

2003042825

Executive Publisher, Global Medicine: Kim Murphy
Executive Director of Development: Lynne Gery
Publishing Services Manager: Frank Polizzano
Senior Project Manager: Robin E. Davis
Associate Developmental Editor: Joanie Milnes
Interior Design: Karen O'Keefe Owens

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

233 OBESITY

Michael D. Jensen

Obesity is the most common nutritional disorder in the United States, costing more that $100 billion per year in health-related expenses. Most physicians do not receive specific training in the evaluation and management of obesity despite the fact that more than half the patients they encounter are likely to be overweight or obese. Although progress has been made in understanding the pathophysiology and treatment of obesity, it nonetheless remains a difficult disease to treat. The safest and most effective treatment approaches (lifestyle and behavior modification) are not those commonly employed by physicians.

Definition

The National Institutes of Health/NHLBI report entitled "Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity" provides clear, scientifically based definitions of overweight and obesity. Body mass index (BMI) is now the recommended means to categorize weight relative to height for adults. Body mass index is calculated as weight (kg) divided by height squared (m^2). To calculate BMI using pounds and inches, the formula is modified as follows: weight (pounds)/height (inches)^2 × 703. The weight classifications according to BMI are summarized in Table 233–1. Individuals who are overweight (BMI 25.0 to 29.9) may or may not be overfat. Some men may be overweight because of increased muscle mass, which is a straightforward clinical judgment. Although in general the risk of developing weight-related health problems increases with a BMI greater than 25, the guidelines point out that intervention or discussion of weight issues with the patient may not be necessary for overweight adults who are entirely healthy and/or are not overfat. On the other hand, some individuals in the BMI 27 to 29.9 range develop serious metabolic complications of obesity that could be expected to improve with weight loss. These individuals are candidates for more aggressive treatment, including pharmacotherapy if needed.

The risk of comorbidities increases considerably once the BMI increases above 30, the level at which obesity is diagnosed. Obesity is divided into three classes, also depending upon BMI. Treatment approaches may differ for those who are overweight and for different classes of obesity. For example, current Food and Drug Administration (FDA) guidelines indicate that pharmacotherapy can be adjunct treatment for any class of obesity, even if medical complications are not present. Although some would argue that treating obese patients without medical complications is a lower priority than treating those with medical complications, familiarity with the guidelines is important; supervisory agencies and third party payers use them to determine who is eligible for treatment benefits. Extreme obesity (BMI >40) is one of the key features that would prompt consideration of a patient for bariatric surgery when medical treatments have failed. Patients with class 2 obesity (BMI 35.0 to 39.9) may be considered for bariatric surgery if medical treatments have failed and if severe, life-threatening complications are present.

The use of BMI to define overweight and obesity is an improvement over previous ideal weight tables, which were based on height/weight percentiles of individuals applying for insurance. In addition to using BMI, the NHLBI Guidelines recommend using the waist circumferences as another office assessment tool that can help with the treatment decision making process. A "large" waist circumference (greater than 102 cm or 40 inches for men and greater than 88 cm or 35 inches for women) is considered an additional indication of risk for overweight and obesity. This measure is primarily relevant to disease risk in overweight and class 1 obesity categories, however. In overweight individuals, a large waist circumference changes the relative risk from "increased" (relative to someone with a normal BMI) to "high." In class 1 obesity, a large waist circumference increases the risk of disease from "high" to "very high." A large waist circumference does not affect disease risk in those persons with class 2 or class 3 obesity.

Table 233–1 ▪ CLASSIFICATION OF OVERWEIGHT AND OBESITY BY BODY MASS INDEX (BMI)

	OBESITY CLASS	BMI (kg/m^2)
UNDERWEIGHT		<18.5
NORMAL		18.5–24.9
OVERWEIGHT		25.0–29.9
OBESITY	I	30.0–34.9
	II	35.0–39.9
EXTREME OBESITY	III	≥40

Prevalence

The number of overweight and obese adults in the United States has increased dramatically over the past 20 years. It is estimated that approximately 60% of adult Americans are either overweight or obese. Approximately 60% of U.S. men and 51% of U.S. women are overweight or obese. It should be noted, however, that a greater percentage of women are obese than men, whereas a larger percentage of men are overweight than women. There are substantial differences in the prevalence of obesity by age, race, and socioeconomic status. The prevalence of obesity in adults tends to rise steadily from ages 20 to 60 years but does not increase and, in fact, begins to decrease in later years. It has been estimated that almost 75% of men aged 60 to 69 years in the United States have a BMI of greater than 25. The increase in mean BMI with age may not be as much of a threat to population health as might first be anticipated. While it is true that young adults with BMIs in the lower part of the normal range have the lowest mortality rates, this changes with age. The BMI associated with the lowest mortality rates is actually at or somewhat above 25 kg/m^2 for those in their 60s and 70s. Clearly, weight recommendations for a given individual depend on whether adverse health consequences associated with obesity have developed.

The differences in overweight and obesity between African-Americans, Mexican-Americans, and European-Americans are not subtle. African-American women and Mexican-Americans of both sexes have the highest rates of overweight and obesity in the United States. When interpreting these data, however, it is important to keep in mind that there is an inverse relationship between socioeconomic status and obesity, especially among women. Women in lower socioeconomic classes are much more likely to be obese than those in higher socioeconomic classes. This association reduces, but does not eliminate, the racial differences in the prevalence of obesity. Whether the remaining racial differences in the prevalence of obesity are due to genetic, constitutional, or social factors not related to income is not yet clear.

Etiology

In one sense, the etiology of obesity can be considered simplistically; if energy intake exceeds energy expenditure, and if lean body mass remains stable, body fat must increase. Unfortunately, obesity is a much more complex issue. There are significant genetic/constitutional susceptibility aspects to obesity that are heavily influenced by environmental factors. Evidence from family studies and studies of twins strongly supports the concept that within a given environment, a significant portion of the variation in weight is genetic. That said, however, the tremendous increase in the prevalence of obesity in the United States over the last several decades can hardly be ascribed to mass changes in human DNA.

GENETIC ASPECTS. There is strong evidence for a hereditary tendency toward the regulation of body weight. The single gene defects resulting in obesity include a number of classic genetic syndromes such as Prader-Willi and Laurence-Moon-Biedl. The reader is referred to textbooks on genetic disorders for a complete list and description of these conditions. More recently, extremely rare monogenic forms of human obesity due to mutations in the leptin gene and leptin receptor gene have been described. The result is an actual or functional leptin deficiency, much like that seen in *ob/ob* or *db/db* mice, the animal models that stimulated the discovery of leptin. There have also been reports of inherited forms of human obesity due to mutations of genes that regulate appetite neuropeptide synthesis. Doubtless, reports of single gene mutations associated with human obesity will continue to appear; however, the overwhelming majority of cases of human obesity are related to the combination of polygenic susceptibility traits and environmental conditions.

CONSTITUTIONAL INFLUENCES. A number of environmental influences can result in long-term, gene-like effects on body weight regulation and the tendency to be susceptible to obesity-related health problems. The effect of the intrauterine environment and the perinatal period on subsequent weight and health is best studied. For example, undernutrition in the last trimester of pregnancy and in the early postnatal period results in a decreased risk of adult obesity. Unfortunately, the low birth weight that is associated with malnutrition in late pregnancy also increases the risk of hypertension, abnormal glucose tolerance, and cardiovascular disease in adulthood. In contrast, undernutrition limited to the first two trimesters of pregnancy is associated with an increased probability of adult obesity. Other early "environmental" effects are that infants of diabetic mothers tend to be fatter than those of nondiabetic mothers, and children of diabetic mothers have a greater prevalence of obesity when they are 5 to 19 years old, independent of their mother's obesity status. Finally, intrauterine exposure to the diabetic environment results in an increased risk of diabetes mellitus and obesity in the offspring. Thus, the issue of the genes versus the environment as regards obesity and metabolic complications of obesity is blurred in the intrauterine and perinatal time intervals. One of the striking and worrisome aspects of these metabolic effects is not only the long-term effects on the individual's weight regulation and health, but the suggestion that these traits can be passed on to future generations.

ENVIRONMENTAL CONTRIBUTORS. Few would argue that there have been dramatic changes in the environment over the last 50 years. These changes promoted a reduction in the amount of physical activity that Americans undertake. In addition, alterations in the food supply have either increased or failed to allow the expected decrease in energy intake that would be needed to match the reduced energy expenditure.

Food. A number of environmental factors can influence food intake (Table 233–2). Consuming energy-dense foods results in greater energy intake, because many adults respond to the volume of food taken in rather than the energy content of food. This factor likely accounts for the association between high-fat diets and excess body weight; many high-fat foods are also energy dense. When humans consume diets that are high in fat but low in energy density, energy intake is not greater than would be expected based on the energy density of the foods. Larger food portion size has also been shown to increase food intake. Given the trend in the United States to serve larger portions of food and beverage, this could be a contributing variable toward obesity. Food variety can also affect energy intake. An increased variety of entrees, sweets, snacks, and carbohydrates in the diet is associated with an increase in body fatness and food intake. In contrast, an increase in variety of vegetables available does not result in an increased food intake and is not associated with increased body fatness. Other factors that may have broad population effects in the United States is the reduced costs of food relative to increased availability and palatability of foods.

Several individual factors may also influence how the properties of food affect energy intake. Individuals vary with respect to their dietary restraint (the tendency to consciously limit food intake to control weight), their feelings of hunger, or their disinhibition (the tendency to overeat opportunistically). It has been proposed that interindividual differences in these factors may modify how food variety, portion size, and so on affect the eating profile. In addition to the environmental influences on food consumption, there are also the effects of the social context under which food is consumed and the emotional state of the individual. These effects are not yet well quantified.

Table 233–2 • ENVIRONMENTAL FACTORS PROMOTING OBESITY

DIETARY	ACTIVITY
↑ energy density of foods	↑ sedentary behavior
↑ portion size	↓ activities of daily living
↑ variety*	↓ employment physical activity
↑ palatability	
↑ availability	
↓ cost	

*Variety of sweets/snacks/entrees

Physical Activity. Physical activity can be broadly divided into exercise (fitness- and sports-related activities) and nonexercise activities. Nonexercise activities include employment-related work and the activities of daily living. Tables are widely available that allow one to calculate energy expenditure based on an individual's weight as well as the type and duration of exercise in which they engage. Unfortunately, only a fraction of Americans engage in exercise at the recommended frequency, intensity, or duration that could be expected to have a protective effect on the development of obesity and other health problems. The portion of Americans who exercise regularly does not appear to be changing; therefore, it seems unlikely that a change in exercise habits over the past several decades is causing the increase in obesity. To the extent that reduced physical activity is contributing to the epidemic of obesity, it is likely the nonexercise component that is changing.

It is difficult to measure the energy expended in nonexercise activity. Although it seems obvious that employment physical activity has decreased with the advent of more automated systems in the workplace, there are surprisingly little data in this regard. One estimate suggests that between 1982 and 1992, energy expenditure at work decreased by approximately 50 kcal/day. The additional changes in the workplace since that time have likely further reduced employment physical activity.

The other component of nonexercise physical activity, the activities of daily living, is equally difficult to measure. A plethora of labor-saving conveniences (e.g., drive-through food and banking, escalators, remote controls, e-mail, on-line shopping) have been introduced into the modern environment. Each of these further reduces the energy humans must expend to get through the day. Again, there are few hard data to assess how much of a change has actually occurred, although a reduction in daily walking trips and an increase in daily automobile trips has been documented.

Perhaps because it is easier to assess, information as to how differences in sedentary activity (television watching, video games, and computer use) relate to obesity is more readily available. There is compelling evidence that more time spent in sedentary pursuits is associated with an increased risk of overweight and obesity. The striking aspect to these studies is that the adverse effect of sedentary activities is independent of participation in traditional exercise activities.

Understanding the contributions of decreased work-related physical activity, decreased activity of daily living, and increases in sedentary behavior can help the physician working with the patient to uncover patterns that may relate to weight gain.

In summary, there are clearly dramatic changes in Western environments that are conspiring to bring out tendencies toward obesity in those with constitutional or genetic susceptibility. Physicians who are aware of these environmental factors are better able to help their obese patients identify which of these environmental factors are contributing to the problem and develop plans for intervention.

Regulation of Body Weight and Energy Balance

Not all of the factors that contribute to the regulation of adult body weight are fully understood; however, this must be a well-balanced process. For example, the typical U.S. adult takes in and expends approximately 2000 to 3000 kcal/day. If there were a consistent error of even 1% in overconsumption of food, this would result in the gain of approximately 25 to 30 pounds of fat every 10 years if there were no change in energy expenditure. Clearly, most adults are able to regulate the average energy balance with much greater precision than 1%. There appears to be regulation both of energy intake and energy expenditure via conscious and unconscious processes.

The excess energy consumed by adults is generally stored as triglyceride in adipocytes. The primary means by which adipose tissue mass expands is to increase the amount of fat stored in each cell (adipocyte hypertrophy). This process can store only a limited amount of fat, however, because there is an upper limit to the size of fat cells. If sufficient fat is deposited, eventually new fat cells are recruited from preadipocytes present in the stromovascular component of adipose tissue. Some adults recruit new adipocytes more readily than others, and thus gain weight more from adipocyte hyperplasia than from hypertrophy. There is evidence that adipose tissue, rather than being static, is slowly but continuously being turned over. Although this may seem surprising, the wide variety of nonfuel activities in which adipocytes are known to participate emphasizes that much of what we once thought we knew about adipose tissue may be incorrect.

The discovery of leptin, a protein secreted by adipose tissue that has potent central nervous system effects on food intake as well as diverse peripheral physiologic actions, led to the hope that the problem of body weight regulation had been solved. The leptin-deficient animal model of obesity, the *ob/ob* mouse, is severely obese, hyperphagic, hypometabolic, and sexually immature and has low levels of spontaneous activity. Administering leptin to this animal corrects all of the above-mentioned defects.

What role does leptin play in human obesity? Reports indicate that virtually all individuals with increased body fat have high plasma leptin concentrations; therefore, leptin deficiency is not a common cause of human obesity. Since the discovery of leptin, only two children, the offspring of consanguineous parents, have been found to have congenital leptin deficiency; they were hyperphagic and severely obese. True human leptin deficiency must be extremely rare. Some animal models of genetic obesity (the *db/db* mouse and *fa/fa* rat) have defective leptin receptors, making them unresponsive to leptin. These observations raised the possibility that human obesity, rather than being a condition of leptin deficiency, is a state of leptin resistance. Although an obese human with a defective leptin receptor gene has been reported, it appears that leptin resistance due to leptin receptor defects (or post-signaling genetic abnormalities) is extremely rare.

Much has been learned about the physiology of leptin in humans. Leptin is secreted in a diurnal fashion that appears to be regulated by the effects of insulin and glucose on adipocytes. Leptin secretion can be increased by 30 to 40% with brief periods of overfeeding (prior to changes in body composition), and is reduced by 50% in response to periods of underfeeding that do not result in significant changes in body composition. These rapid and substantial shifts in leptin secretion can potentially account for a large portion of the variability in the normally strong relationship between percentage of body fat and serum leptin concentrations. When blood is collected under carefully controlled circumstances, there is a very strong relationship between plasma leptin concentrations and percentage of body fat (Fig. 233–1). There is no difference in the relationship between leptin and percentage of body fat between women and men. Thus, the assertion that leptin resistance is present in women and in human obesity is not logical; if the normal biologic response to increased body fat is increased leptin secretion, hyperleptinemia merely becomes a different definition of fatness/obesity. Only when deficiency is present does its physiology relate to the development of obesity.

Low or absent leptin results in extreme hunger. Treating patients with congenital leptin deficiency with physiologic doses of recombinant leptin resulted in a remarkable reduction in excessive hunger and significant fat loss. In contrast, treatment of overweight patients with recombinant leptin did not show weight loss, despite achieving peak serum leptin concentrations greater than 30 times basal levels. In animals, leptin plays an important role in modulating the hypothalamic-pituitary response to undernutrition and serves a protective function. Human studies are necessary to confirm this observation. Several of the observed effects of exogenous leptin in *ob/ob* mice were not observed in the single case of human leptin deficiency treated with leptin. In summary, the discovery of leptin has been an important advance in understanding the biology of obesity; however, defects in leptin secretion or inherited defects in leptin action do not appear to be the cause of even a tiny fraction of human obesity.

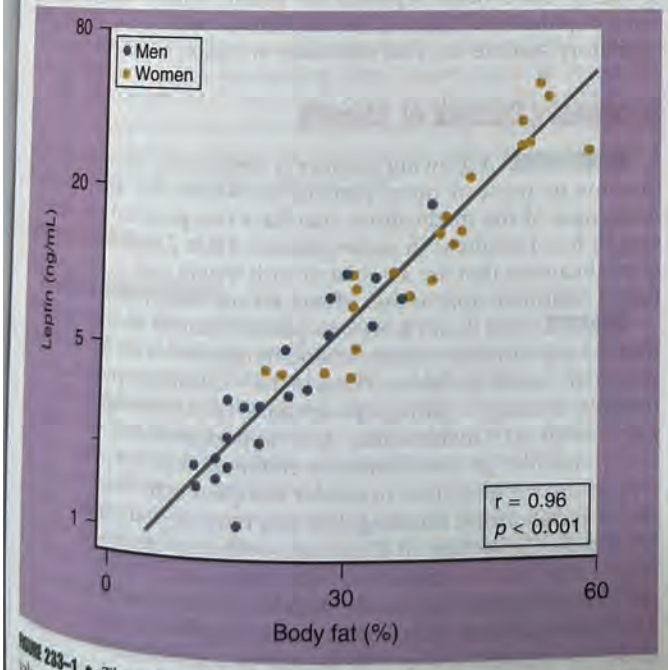

FIGURE 233–1 • The relationship between serum leptin concentrations (log values) and percentage of body fat in 43 lean and obese men and women. (Adapted from Jensen MD, Hensrud D, O'Brien PC, et al: Collection and interpretation of plasma leptin concentration data in humans. Obes Res 1999;7:241–245. © 1999 North American Association for the Study of Obesity. All rights reserved).

ENERGY INTAKE

Much has been learned about the biologic regulation of food intake, mostly from the study of animal models. There are a series of peripheral "satiety" signals that act to inhibit further food intake at some point during meal consumption. Some of the signals reach the brain via the vagus nerve and some via the systemic circulation. Examples of the proposed humoral factors modulating appetite are listed in Table 233–3. Many of the compounds are gut- or pancreas-derived hormones (cholecystokinin, glucagon-like peptide 1, insulin, and perhaps other glucagon-related peptides or gut peptides) or peptides (apolipoprotein A-IV, secreted with chylomicrons). The signals are thought to be triggered both by mechanical stimuli (e.g., the fullness of the stomach) and by the presence of nutrients in the jejunum and ileum. It has also been suggested that the drop in leptin concentrations at night may allow the evolution of hunger the following morning.

The central nervous system regulation of food intake is also better understood. A series of neuropeptides and monoamines have been identified that have either anabolic (increased food intake with or without decreased energy expenditure) or catabolic (decreased food intake with or without increased energy expenditure) properties. A list of these compounds is provided in Table 233–4. Understanding

Table 233–3 • SUGGESTED BIOLOGIC MODULATORS OF FOOD INTAKE

PERIPHERAL SIGNAL	PROPOSED EFFECT ON FOOD INTAKE
Vagal	(–)
Cholecystokinin	(–)
Apolipoprotein A-IV	(–)
Insulin	(–)
Glucagon-like peptide 1	(–)
Other glucagon related peptides	(–)
Leptin	(+) when leptin ↓↓
Ghrelin	(+)
Tumor necrosis factor-α	(–)
PYY	(–)

(–) inhibits food intake.
(+) stimulates food intake.

Table 233–4 • CENTRAL NERVOUS SYSTEM MODULATORS OF ENERGY BALANCE

CENTRAL ANABOLIC (↑ FOOD INTAKE)	CENTRAL CATABOLIC (↓ INTAKE)
Neuropeptide Y	α-Melanocyte stimulating hormone
Agouti-related protein	Corticotropin releasing hormone
Melanin-concentrating hormone	Thyrotropin releasing hormone
Hypocretins/orexins	Cocaine- and amphetamine-regulated transcript (CART)
Galanin	Interleukin-1β
Norepinephrine	Urocortin
	Oxytocin
	Neurotensin
	Serotonin

the process of appetite regulation may allow the discovery of therapeutic agents that will selectively inhibit or stimulate either anabolic or catabolic central nervous system pathways.

ENERGY EXPENDITURE

Daily energy expenditure in adults varies widely, from less than 1400 kcal/day to more than 5000 kcal/day, with larger, more physically active individuals having the greatest energy needs. Typically, daily energy expenditure is divided into resting (or basal) metabolic rate, the thermic effect of food, and physical activity energy expenditure.

BASAL METABOLIC RATE. The basal metabolic rate (BMR) is the energy expenditure of lying still at rest, awake, in the overnight postabsorptive state. A true BMR is measured after awakening but prior to arising from bed. The resting metabolic rate (RMR) is similarly defined but is not necessarily measured before arising from bed. For most sedentary adult Americans, the RMR represents the major portion of energy expended during the day and may range from less than 1200 to more than 3000 kcal/day. Most (approximately 80%) of the BMR can be related to the amount of lean tissue an individual has.

Not all components of lean tissue consume oxygen at the same relative rates. Visceral, or splanchnic bed, tissues account for approximately 25% of resting metabolic rate but a much smaller proportion of body weight. The brain, which accounts for only a small percent of body weight, accounts for almost 15% of RMR. Likewise, the heart (approximately 7%) and kidneys (approximately 5 to 10%) account for greater portions of resting energy needs than their relative contribution to body mass. In contrast, resting muscle makes up 40 to 50% of lean tissue mass but accounts for only 25% of RMR. This changes dramatically with exercise, however; muscle can account for 80 to 90% of energy expenditure during high-intensity exercise. Adipose tissue is a minor contributor to daily energy expenditure, consuming only approximately 3 kcal/kg/day.

Although the vast majority of RMR can be accounted for by the amount of lean tissue an individual has, there are also other, more subtle, influences on RMR. Age, gender (women have slightly lower BMRs, even corrected for fat-free mass), and fat mass affect RMR. Slight changes in metabolic rate or BMR are observed during the menstrual cycle (luteal phase more than follicular phase). There is also evidence that heritable or family factors do influence BMR, accounting for as much as 10% of interindividual differences.

There are both obligatory and facultative components to RMR. With an energy-restricted diet, significant reductions in BMR relative to the amount of fat-free mass occur. Reductions in the production of triiodothyronine from thyroxine are thought to contribute to this phenomenon. Likewise, during brief periods of overfeeding, it has been found that RMR increases above that which would be expected for the amount of lean tissue present.

It has been proposed that individuals with BMRs lower than predicted are at increased risk of future weight gain. Published data suggest that the relative risk is small, and the clinical effort to identify such patients is not warranted. Measurement of BMR is sometimes helpful in the evaluation of patients who insist they are unable to lose weight while following diets consisting of less than 1000 kcal/day. Almost without fail, their BMR is substantially greater than their reported food intake. This underscores the fact that most adults are notoriously unreliable in assessing their own food intake.

THERMIC EFFECT OF FOOD. Approximately 10% of the energy content of food is expended in the process of digestion, absorption, and metabolism of nutrients. There is significant interindividual variability in this value, ranging from a low of approximately 5% to a high of approximately 15% of meal calories that are "wasted" in the postprandial interval. The thermic effect of a meal is related to the carbohydrate and protein caloric content of the meal (the fat content has little stimulatory effect). Both obligatory and facultative components of the thermic effect of food have been identified. The obligatory components no doubt reflect the energy costs of digestion, absorption, and storage of nutrients. Approximately 60 to 70% of the thermic effect of meals is obligatory, and the remaining 30 to 40% is facultative thermogenesis. The two factors thought to play a role in the facultative component of the thermic effect of food are the postprandial insulin response and activation of the sympathetic nervous system. The thermic effect of food is somewhat lower in insulin-resistant/obese humans, but there have been no reported links between reduced postprandial thermogenesis and future obesity.

PHYSICAL ACTIVITY ENERGY EXPENDITURE. The energy expenditure of physical activity is a product of the amount of work done and the work efficiency of the individual. Because there is not much variability in work efficiency, the published values for estimating the energy costs of work performed are quite accurate. It is common to express the work unit as metabolic equivalents, or METs, which is a multiple of the resting metabolic rate. If an individual's RMR is 1 kcal/min, a workload of 5 METs would be 5 kcal/min. Highly trained athletes can work at extremely high METs (>16) for extended periods, but most sedentary individuals can only work for a limited time at much lower workloads. The peak work capacity refers to the maximum number of calories (or maximum amount of oxygen that can be consumed, $\dot{V}O_{2max}$) that can be expended. There is tremendous variability in peak work capacity that is largely, but not solely, related to how much and what type of physical activity is performed.

Another important concept in understanding the capacity for physical activity (and thus exercise prescriptions) is the lactate threshold. The lactate threshold can be thought of as the level at which exercise begins to become so uncomfortable that it cannot be maintained much longer. The biochemical definition relates to the progressive rise in blood lactate concentrations that are observed. The lactate threshold may range from 50% to 90% of an individual's peak work capacity. Training raises the lactate threshold closer to the maximum workload, and thus allows individuals to work at higher rates for longer periods of time. Obese, sedentary individuals typically have lactate thresholds that are quite low (sometimes on the order of 4 to 5 METs), and the threshold can be even lower in obese patients with type 2 diabetes.

Exercise (fitness- and sports-related activities) is commonly considered the main component of physical activity thermogenesis. Although a large amount of energy can be expended in relatively brief periods in fit individuals, most adults do not exercise at high levels or for a sufficient duration to expend a large amount of energy. Thus, rather than focusing solely on "exercise" as the main component of physical activity energy expenditure, it is important to consider the energy costs of nonexercise activity.

Nonexercise activity thermogenesis (NEAT) is the caloric expense of performing all activities other than exercise. The range of observed NEAT under controlled (metabolic chamber) conditions has been from less than 100 up to approximately 800 kcal/day. There is probably a much wider range in free-living individuals. NEAT is not a static component of daily energy expenditure. It has been shown that NEAT can increase in response to increased food intake in an unconscious manner. In fact, modulation of NEAT can be a significant factor that acts to stabilize weight despite variations in food intake. Low levels of NEAT have been reported to predict future weight gain in some populations. There is virtually no information as to what the regulatory systems are that stimulate or inhibit NEAT.

Secondary Causes of Obesity

MEDICATIONS. A growing number of medications cause weight gain in some or most of those patients for whom they are prescribed. Awareness of the medications that have this potential can facilitate weight loss treatment in some patients. Table 233–5 lists a number of medications that are associated with weight gain as well as alternative treatment approaches, if any, for the underlying condition.

DISEASES. Less than 1% of obese patients have an underlying disease that can explain their obesity. Endocrinopathies are the most common secondary cause of obesity. These include Cushing's syndrome, hypothalamic damage resulting in overeating (most commonly after pituitary surgery), insulinoma, and hypothyroidism. A Cushing's syndrome–like fat distribution is common; therefore, other patient aspects are the best clues to test for this condition. These include the classic purple striae, thinning skin, easy bruising, and proximal muscle weakness. Correction of Cushing's syndrome commonly results in substantial loss of excess body fat. Insulinoma is a rare tumor, and only a small portion of patients with insulinoma present with obesity; only some patients consciously prevent spells by eating more often, and thus become obese. The weight gain associated with hypothyroidism is virtually always due to fluid retention and resolves dramatically with thyroid hormone replacement. Unfortunately, successful treatment is not available for hyperphagia due to hypothalamic damage. Occasionally, adult patients with growth hormone deficiency, most commonly after hypophysectomy, lose excess weight with growth hormone replacement therapy.

Table 233–5 • PHARMACOLOGIC INFLUENCES IN WEIGHT GAIN, AND ALTERNATIVE THERAPIES

DRUGS THAT MAY PROMOTE WEIGHT GAIN	ALTERNATIVE TREATMENTS WITH LESS OR NO WEIGHT GAIN OR THAT PROMOTE WEIGHT LOSS
Psychiatric/Neurologic Medications	Alternative Psychiatric/ Neurologic Medications
Antipsychotics	
Zyprexa, Clozaril	Ziprasodone, risperadone, quetiapine
Antidepressants	
Serotonin reuptake inhibitors, tricyclic antidepressants, monamine oxidase inhibitors	Buproprion, nefazodone
Antiepileptic drugs	
Gabapentin, valproate, carbamazapine	Topiramate, lamotrigine
Lithium	
Steroid Hormones	Alternative to Steroid Hormones
Hormonal contraceptives	Barrier methods
Corticosteroids	Nonsteroidal anti-inflammatory drugs
Progestational steroids	Weight loss
Anti-Diabetes Agents	Alternative Anti-Diabetes Agents
Insulin	Metformin
Sulfonylureas	Acarbose, miglitol
Thiazolidinediones	Orlistat, sibutramine
Antihistamines	Decongestants, inhalers
Antihypertensive Agents	Alternative antihypertensive Agents
α- and β-adrenergic receptor blockers	Angiotensin-converting enzyme inhibitors, calcium channel blockers
Highly Active Antiretroviral Therapy	

Adapted from Wadden T. Stankard AJ, eds: Handbook of Obesity Treatment. Lj Aronne, 2002, p 385.

PSYCHOSOCIAL ASPECTS OF OBESITY. Sexual, physical, and emotional abuse, especially in women, can result in long-term adverse consequences that include obesity. The effects of the abuse tend to be most profound if it occurred in childhood and adolescence. These women may be severely obese, suffer from chronic depression, and experience a number of psychosomatic symptoms, particularly chronic gastrointestinal distress. Identifying these issues prior to initiation of weight loss programs is important because successful weight loss may actually aggravate the distress experienced by these women. In addition, appropriate referral for psychiatric help may be needed prior to initiation of treatment for obesity.

Pathophysiology

METABOLIC COMPLICATIONS. The properties of excess adipose tissue that contribute to the metabolic complications of obesity are now better understood. A key observation was that a central or upper body fat distribution, more so than total fat mass, is predictive of the metabolic complications of obesity. It was also noted that obese individuals with enlarged fat cells (adipocyte hypertrophy) were more likely to suffer the metabolic complications than obese persons with normal-sized fat cells (adipocyte hyperplasia). In vitro studies showed that lipolysis, which results in the release of fatty acids and glycerol, is less well regulated in large adipocytes than in normal-sized adipocytes. The finding that upper body obesity is associated with adipocyte hypertrophy and lower body obesity is associated with adipocyte hyperplasia provided a potential link between fat distribution differences and adipose tissue function as regards its fuel export function.

Adipose tissue release of free fatty acids (FFAs) and glycerol into the circulation via lipolysis provides the majority (in a kinetic sense) of circulating lipid fuel. Lipolysis is capable of providing 50 to 100% of daily energy needs. Adipose tissue lipolysis is regulated primarily by insulin (inhibition) and catecholamines (stimulation), although growth hormone and cortisol also can stimulate lipolysis to a lesser extent. Upper body obesity is associated with several abnormalities of adipose tissue lipolysis, most remarkably with higher FFA concentrations due to excess release in the postabsorptive and postprandial periods. Abnormally high FFA concentrations can contribute to or account for a number of the metabolic complications of obesity.

Insulin Resistance. The term *insulin resistance* is typically used when referring to the ability of insulin to promote glucose uptake, oxidation, and storage as well as to inhibit the release of glucose into the circulation. The primary site of insulin-stimulated glucose uptake, oxidation, and storage is skeletal muscle. The principal site of glucose production is the liver. Insulin resistance initially leads to hyperinsulinemia, a possible independent cardiovascular risk factor, and may eventually lead to the development of type 2 diabetes mellitus.

The ability of insulin to stimulate glucose disposal in muscle (and thus maintain normal glucose tolerance) and suppress plasma FFA concentrations is reduced in cases of upper body obesity. High plasma FFA concentrations can induce a state of insulin resistance both in the muscle (glucose uptake) and in the liver (glucose release), independent of obesity. Thus, abnormal regulation of adipose tissue FFA export can potentially explain much of the insulin resistance with respect to glucose metabolism. Although it has been suggested that production of tumor necrosis factor–α (and other peptides) by fat cells may play a role in the development of insulin resistance, there is little experimental evidence from human studies to support this theory.

Islet Cell Failure/Type 2 Diabetes Mellitus. The development of type 2 diabetes requires defects in both insulin secretion and insulin action. Many obese individuals are insulin resistant, yet only a subset develop diabetes mellitus. It follows that those who develop type 2 diabetes develop pancreatic beta cell decompensation with subsequent hyperglycemia. Animal (rodent) studies have suggested that a process referred to as "lipotoxicity" is involved in pancreatic β-cell failure. In this model, increased FFAs are proposed to contribute to the insulin secretory abnormalities seen in obesity and ultimately lead to beta cell failure. Although FFAs have been shown to modulate insulin secretion, it has not been demonstrated that FFA concentration has long-term adverse effect on islet β-cell function in humans. There are a number of important differences between rodent models of diabetes and human diabetes that require consideration of other possibilities. Another explanation for the development of β-cell failure in obesity is the overproduction of islet amyloid polypeptide. This protein is cosecreted with insulin and, because of its tertiary structure (which is different in humans and rodents), can form toxic amyloid deposits in β-cells. Amyloid deposits have been found in the pancreatic islets obtained at autopsy from patients with type 2 diabetes mellitus.

Hypertension. Blood pressure can be increased by a number of mechanisms. Increased circulating blood volume, abnormal vasoconstriction, decreased vascular relaxation, and increased cardiac output may all contribute to hypertension in obesity. The effect of hyperinsulinemia to increase renal sodium absorption has been proposed to contribute to hypertension via increased circulating blood volume. Abnormalities of vascular resistance may also contribute to the pathophysiology of obesity-related hypertension. Under some experimental conditions, elevated FFA levels have been found to cause increased vasoconstriction and reduced NO-mediated vasorelaxation, similar to that seen in the metabolic syndrome. It has also been suggested that there is an increased activity of the sympathetic nervous system in some obesity phenotypes, and that this contributes to obesity-associated hypertension. There are at least two other issues related to the hypertension of obesity that deserve mention. Tumor necrosis factor-α (produced by adipocytes and preadipocytes) has been suggested to contribute to elevated blood pressure, and angiotensinogen (also produced by adipocytes), a precursor of the vasoconstrictor angiotensin II, is positively correlated to blood pressure in some studies.

Dyslipidemia. Upper-body obesity and type 2 diabetes mellitus are associated with increased triglycerides, decreased high-density lipoprotein (HDL) cholesterol, and a high proportion of small, dense low-density lipoprotein (LDL) particles. This dyslipidemia contributes to the increased cardiovascular risk observed in the metabolic syndrome. Fasting hypertriglyceridemia is caused by increased hepatic secretion of very low density lipoprotein (VLDL). The elevated VLDL secretory rate may well be driven by increased delivery of FFAs to the liver (see earlier), which increases triglyceride synthesis and subsequently VLDL apoB-100 secretion. Low HDL cholesterol and the increase in small, dense LDL particles are likely an indirect consequence of elevated triglyceride-rich VLDL mediated via increased

cholesterol ester transfer protein (CETP) and hepatic lipase activity. Genetic influences play a significant role in the expression of these lipid abnormalities. Polymorphisms in the genes for apolipoprotein E, lipoprotein lipase, apolipoprotein B-100, and apolipoprotein A-II are reported to affect the expression of increased triglycerides and decreased HDL of upper-body obesity.

Endocrine Manifestations. Obesity can create some abnormalities of the endocrine system. One of the most common abnormalities is polycystic ovarian syndrome (PCOS), which is characterized by mild hirsutism and irregular menses or amenorrhea with anovulatory cycles. It is most commonly linked with obesity and often improves with weight loss and/or other treatments that improve insulin resistance. Thus, it is thought that the insulin resistance associated with obesity may trigger the development of PCOS in susceptible individuals.

Mild to moderate androgen overproduction is a feature of upper body obesity in women; however, in men obesity can be associated with mild hypothalamic hypogonadism. There have been some suggestions that treatment of this central hypogonadism with exogenous testosterone is beneficial, but this is not common practice.

Although estrogens are not elevated in obese premenopausal women, they remain somewhat above postmenopausal levels in obese postmenopausal women. This may contribute to some of the increased prevalence of malignancies (see later).

MECHANICAL COMPLICATIONS OF OBESITY. The excess body weight associated with obesity is thought to be responsible for the increased prevalence of lower extremity degenerative joint disease seen in obese patients. Extreme obesity can result in very premature degenerative joint disease, and this may be especially difficult to treat surgically given the greater stress on joint replacements. Severely obese individuals may also have severe problems with venous stasis, which is occasionally aggravated by right heart failure (see later).

Obstructive Sleep Apnea. Sleep apnea is quite common in severely obese patients, tending to be more common in men generally and in women with an upper body obese phenotype. Sleep apnea is most likely explained by enlargement of upper airways soft tissue, resulting in collapse of the upper airways with inspiration during sleep. The obstruction leads to apneas, with hypoxemia, hypercarbia, and a stress response (high catecholamine and endothelin levels). The frequent arousals to restore breathing result in poor sleep quality. Sleep apnea is associated with an increased risk of hypertension, and, if sleep apnea is severe, it can lead to right heart failure and sudden death. A history of daytime hypersomnolence, loud snoring, restless sleep, or morning headaches is suggestive of obstructive sleep apnea.

Cancer. The risk of breast cancer and endometrial cancer is increased in obese women. It is thought that this may be due to the increased estrogen levels associated with obesity in postmenopausal women. Obese men also have a higher rate of mortality with cancers of the prostate and colon. The reasons for this association are unknown.

Gastrointestinal Disorders. Gastroesophageal reflux disease and gallstones are more prevalent in obese patients. Likewise, fatty liver and nonalcoholic steatohepatitis is more common in obese patients. Nonalcoholic steatohepatitis can eventually progress to cirrhosis and can be a fatal. Weight loss and interventions that improve insulin sensitivity appear to improve fatty liver and nonalcoholic steatohepatitis.

Evaluation

In the office practice, obtaining an accurate height and weight allows calculation of BMI, and under some circumstances measurement of the patient's waist circumference can be useful in assessing risk (see earlier). Accurate measure of blood pressure, which may require a large blood pressure cuff, is important. Identification of the adverse health consequences of obesity should be a routine part of office evaluation of a patient who is overweight or obese. The presence or absence of dyslipidemia (HDL cholesterol <45 mg/dL for women, HDL cholesterol <35 mg/dL for men, or triglycerides >150 mg/dL), hypertension, glucose intolerance/diabetes, and hyperuricemia should be documented. The presence of three or more of these health problems (or two with evidence of insulin resistance) is considered criteria for diagnosis of the dysmetabolic syndrome X. A history suggestive of sleep apnea should prompt a referral for overnight oximetry or a sleep disorder evaluation.

After determining the level of health risk facing the patient with obesity, a review of the patient's lifestyle, including an assessment of physical activity level and eating habits, may help provide information about why the patient is obese. A family history of obesity, or long-standing obesity, provides evidence that there is not a secondary cause of obesity. A careful medication history and social history may help the clinician identify precipitating factors that can be modified to enhance the success of treatment.

Prior to the patient's entering a weight management program, it is important to ensure that he or she has realistic goals and expectations. Often patients expect to lose large amounts of weight in short periods of time with little or no effort. Medical treatment programs, even if they include pharmacotherapy, do not often result in greater than 10% weight loss. A 10% weight loss, however, is sufficient to markedly reduce the medical complications of obesity, although a patient disappointed with this result may quit a medically successful program. Helping the patient to realize and accept that 10% weight loss is reasonable can be one of the more challenging aspects for a physician but can prevent unnecessary disappointment later on.

It is sometimes necessary to delay entry into treatment programs if a patient is not ready to make changes in his or her lifestyle. In this case, a reasonable strategy is to periodically remind the patient of the potential health benefits of improved activity and eating habits. Once a willingness to make changes is apparent, treatment is more likely to succeed.

Rx Treatment

Obesity represents an individual's response to the environment based on genetics and learned behavior. It is seldom a temporary condition and is best viewed as a chronic disease. Therefore, treatment must be considered a long-term issue, much like treatment of diabetes, hypertension, or dyslipidemia. Substantial weight loss can be induced via severe caloric restriction, but without approaches to ensure behavioral changes body fat is invariably regained. Permanent lifestyle changes (eating and activity behavior) can result in permanent weight loss.

Reducing energy intake is the most efficient and effective means to lose weight. For example, creating a 500 kcal/day deficit via reduced food intake can allow the loss of 1 lb of fat per week. Although possible, it is much more difficult to increase energy expenditure by 500 kcal/day through exercise. Higher levels of physical activity can prevent weight gain (or weight regain after weight loss). Some patients are able to change eating and activity habits on their own given the proper information, whereas others require behavior modification interventions (formal or informal) to help make these changes. In some instances, pharmacotherapy or surgery may be needed for treatment of obesity. Figure 233–2 shows how to evaluate and manage overweight and obese patients.

DIET. Changes in eating habits must be permanent if weight loss is to be maintained. An experienced registered dietitian can be helpful in the evaluation of a patient's eating habits and will be able to provide the needed education. The diet history may identify a few eating behaviors that are resulting in excess energy intake. Specific recommendations can then focus on the most blatant poor eating habits. In addition to addressing particular adverse eating behaviors, there are some general principles regarding diet that should be addressed. Reducing the energy density of food (most commonly accomplished by reducing dietary fat) can allow patients to feel satiated while consuming fewer calories. A common mistake, however, is for patients to consume large quantities of easy to eat "non-fat" foods, thereby offsetting the expected benefits of the diet. In addition to reducing the intake of high-fat foods, patients should understand that increasing the consumption of foods high in water and fiber (fruits, vegetables, legumes, and soups) can provide satiety without excess calories. It is also important to avoid the excess intake of beverages containing substantial calories with little or no satiety. Finally, a regular pattern of eating should be encouraged.

New, fad diets are continuously being promoted with the promise of easy weight loss. A common feature of these diets is the claim that special properties of certain foods help people lose weight or are the cause of obesity. If followed, most of these diets result in weight loss because of a reduced energy intake. The reduced intake can be related to the monotony of the diet or, in the case of the low carbohydrate diets, to the appetite suppressant effect of ketosis.

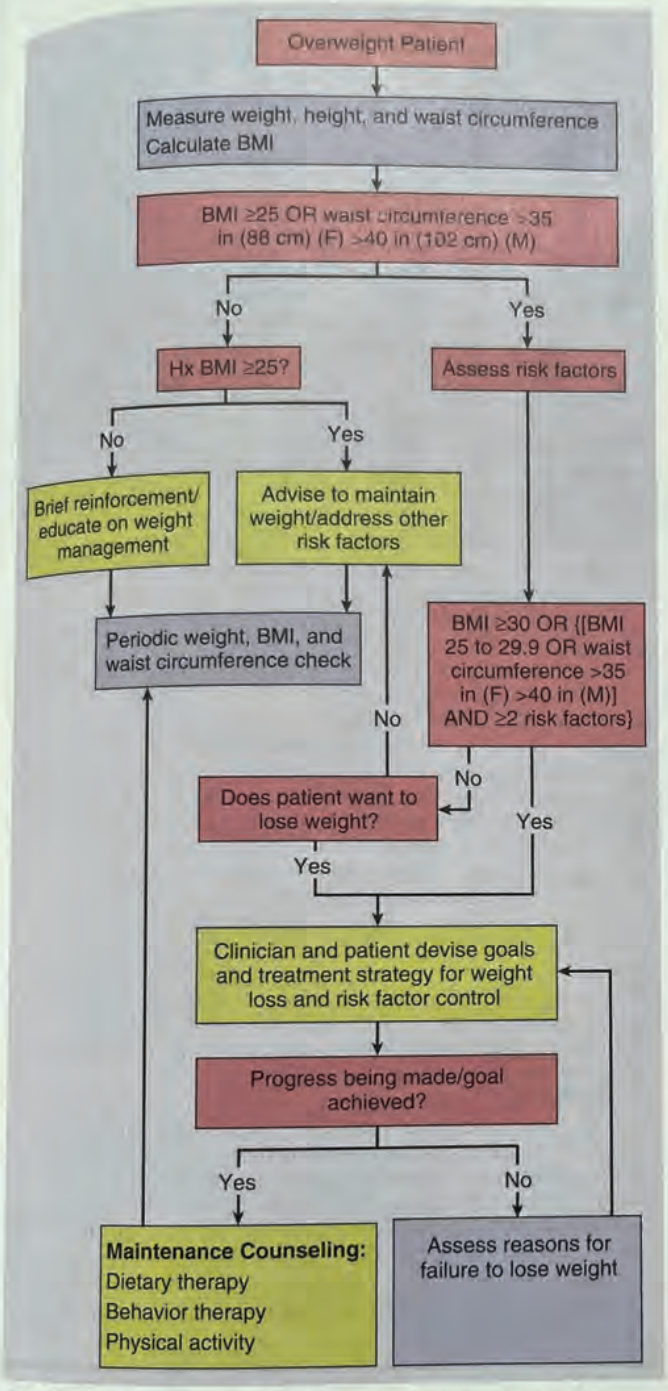

FIGURE 233–2 • Flow diagram for the evaluation and management of overweight and obesity. BMI = body mass index. (Adapted from the NIH/NHLBI: Clinical Guidelines on the Identification, Evaluation and Treatment of Obesity in Adults: The Evidence Report. Obes Res 1998;6:51S–209S).

In small randomized trials, low carbohydrate diets have been at least as effective as conventional diets for weight loss.

Very low calorie diets (less than 800 calories per day) have been used for years to achieve accelerated weight loss. The rationale for this approach is now in question, given that the long-term results of these diets is no better and sometimes worse than the results from the standard low-calorie diet combined with behavior modification. The expensive laboratory monitoring required for very low calorie diets without an improved long-term outcome raises questions as to the cost-to-benefit ratio of this approach.

PHYSICAL ACTIVITY. Long-term increases in physical activity are necessary to prevent weight regain following successful weight loss. Unfortunately, many overweight and obese patients are quite unfit, being unable to walk even 1 mile continuously. It is not possible for most adults to burn large numbers of calories. For example, only approximately 100 kcal are expended by a 70 kg adult walking 1 mile. Losing weight solely by increasing exercise is impractical for most patients. Increasing physical activity as a means of maintaining weight loss is an attainable goal for most patients, however.

Successful maintenance of weight loss requires that daily energy expenditure be an average of 80 to 90% above RMR. This is a considerable increase for most patients. For example, someone with an RMR of 1500 kcal/day would need to expend approximately 1000 kcal/day in physical activity to meet this target. Activities other than "exercise" are important means to achieve this goal.

There are important health benefits from regular physical activity over and above the effects on weight. These include lower rates of cardiovascular and all-cause mortality, independent of weight. The options for increasing physical activity include exercise (sports or fitness pursuits) or using lifestyle approaches. Both methods can improve fitness and allow weight stability, although persuading obese patients to become more active is not easy. Physicians can begin by asking patients about their current and past activity habits, as well as what barriers they see to increasing physical activity. This accomplishes the goal of stimulating patients to think about the issue in a tactful manner. It can help to ask the patient what personal benefits they envision as a result of increasing their level of activity. If patients agree to begin a exercise/physical activity program, they will need to monitor their activity and set realistic goals for the amount of exercise they are going to achieve.

BEHAVIOR MODIFICATION. Patients who are unable to make changes in eating activity habits on their own or with informal office counseling may benefit from referral to a behavioral therapist. The goals of behavior modification are to help patients modify their eating, activity, and thinking habits that predispose to obesity. The goals of behavioral therapy focus on achieving selected results as regards eating and activity habits and focusing on specific pathways on how to achieve the goals. These pathways may include identifying and removing barriers to developing better eating or activity habits. Small, incremental and consistent changes in behavior are encouraged, as opposed to large, inconsistent changes in behavior. Self-monitoring of food and activity is considered a key feature to success, because most obese patients underestimate food intake and overestimate exercise in the absence of objective measures. Cognitive restructuring has been introduced as a way to help overcome the thought processes that can lead to failure of a weight management program. Patients are taught to identify, challenge, and correct self-defeating thoughts.

PHARMACOTHERAPY. A limited number of drugs are currently available to help patients with weight loss. The disastrous experience with fenfluramine and dexfenfluramine (pulmonary hypertension and cardiac valvular disease) has clearly dampened the enthusiasm of many physicians to prescribe weight loss drugs, even under circumstances that justify their use. Not all overweight or obese patients are candidates for pharmacologic treatment. Table 233–6 provides criteria to help select patients for pharmacologic treatment. Because pharmacologic treatment of obesity exposes patients to some risks and expense, it is reasonable to require an objective benefit. A rational argument can be made that priority should be given to those patients with one or more medical complications or conditions that are likely to improve with weight loss. Medications should not be used alone, but only as a part of a comprehensive program that includes diet, exercise, and behavior modification. When prescribing antiobesity medications, it is important to set clear goals with respect to both weight loss and health benefits. Just as with other classes of medications, continued use of ineffective or suboptimally effective drugs does not serve the patient.

Current Medications. The medications currently available for long-term use act either through appetite reduction (e.g., sibutramine) or via inhibition of intestinal lipase (resulting in fat malabsorption). Phentermine, an appetite suppressant, is currently approved for short-term (3 months) use. Because weight that is lost with

Continued

Table 233–6 • INDICATIONS FOR PHARMACOLOGIC TREATMENT OF OBESITY

Body mass index >27 kg/m^2
One or more complications or conditions that are likely to improve with weight loss
Previous failure of conservative treatment with diet and exercise
Patient agrees to 2- to 4-week trial of making initial changes in diet and exercise before starting pharmacotherapy
Patient agrees to continued treatment with diet, exercise, and behavioral modification while on pharmacologic treatment
Patient agrees to periodic follow-up
Premenopausal women (able to have children) must use some form of contraception
Consider a pregnancy test when initiating treatment if any possibility of pregnancy
No contraindications to the specific drug used for pharmacologic treatment

pharmacotherapy (especially when used without a comprehensive program) is quickly regained once the medication is discontinued, agents that are approved for long-term use (sibutramine and orlistat) are more rational therapeutic choices.[2]

Sibutramine also acts via appetite regulation mechanisms. Patients are typically not less hungry but do experience earlier satiety, resulting is less food intake. The usual starting dose for sibutramine is 10 mg in the morning, with maximum dose of 15 mg if the response is suboptimal. Monthly monitoring for the first 3 months is needed to ensure a good response and to detect adverse effects. A minority of patients develop cardiovascular responses (hypertension and tachycardia) that contraindicate continued use of the medication. Failure to lose weight over the first 1 to 2 months is a strong indicator of drug treatment failure and should prompt the physician to discontinue sibutramine.

Orlistat, a pancreatic lipase inhibitor, facilitates weight loss through a different mechanism. At the typical dose of 120 mg three times daily with meals, approximately 30% of dietary fat is malabsorbed. As expected, adverse gastrointestinal side effects occur. These including oily spotting, abdominal pain, excess flatus, and fecal urgency, together with fatty or oily stools. These side effects decrease with continued use. There is evidence that concomitant use of bulk-forming laxatives (e.g., psyllium, methylcellulose) can reduce the side effects. It is not necessary to use orlistat if a non-fat meal is being consumed.

Both sibutramine and orlistat improve the results of medical treatment programs that include diet, exercise, and behavior modification.[3,4] The addition of either agent results in almost twice as many patients achieving goal weight loss (10% of body weight). There appears to be no additive effect of sibutramine and orlistat.

Success of Medical Therapy. It has been estimated that more than 95% of patients embarking on self-diets or fad diets fail to maintain a significant weight loss for a period of time that would have meaningful health benefits. The published results of commercial programs are not impressively better, mostly because of high dropout rates. In contrast, organized, scientifically based weight management programs that employ behavior modification in addition to dietary instruction, physical activity, and medications (when indicated) can achieve impressive results. Although these programs tend to be more selective (accepting only motivated patients), the dropout rates can be acceptable (<30%) and of those remaining in the program a greater than 10% weight loss can be achieved and maintained for more than 1 or 2 years in 40 to 60% of patients. These results are more impressive than those reported with older, less comprehensive programs, wherein almost all patients regained all weight in less than 6 months.

BARIATRIC SURGERY. Surgical treatment is indicated for severely obese patients with severe medical complications that could be expected to improve with successful weight loss. Patients with a BMI of 35 to 40 with life-threatening complications can be considered, but more typically patients with a BMI greater than 40 and several complications are candidates for surgery, assuming past attempts at medical treatment have failed. Because the risks and costs of surgical treatment are greater than for medical treatment, it is reasonable practice to select patients who stand to obtain more potential benefit from surgery. Contraindications to surgery include active substance abuse, defined noncompliance with previous medical care, and certain psychiatric disorders (schizophrenia, borderline personality disorder, uncontrolled depression).

A multidisciplinary team, including a physician, dietitian, psychologist or psychiatrist with expertise in this area, and a surgeon experienced in bariatric procedures, is important for optimal outcome. Defining realistic expectations is an important part of the evaluation process. Patients undergoing bariatric surgery are not likely to be reduced to their ideal body weight. Successful weight loss is typically defined as losing an average of 50 to 60% of excess body weight; that is, if someone is 150 kg overweight, they might reasonably be expected to lose 75 kg.

A variety of bariatric surgical procedures have been used. The jejunoileal bypass has been abandoned because of delayed severe complications, including liver failure, renal failure, and arthropathy. If these complications are identified, reversal of the procedure can improve or stabilize organ function. Several gastric procedures (gastroplasty, vertical stapling, vertical banded gastroplasty, and gastric banding) are commonly used but are less effective than the roux-en-Y gastric bypass in terms of long-term weight loss and outright surgical failure. A procedure termed the *partial pancreaticobiliary bypass* has become popular in some areas but is associated with sometimes severe, even fatal vitamin and mineral deficiencies.

The results of the roux-en-Y gastric bypass for treatment of morbid obesity have been impressive. Approximately 80% of patients achieve success, as defined above, with this procedure. The mortality (<1%) and morbidity (e.g., infection, wound dehiscence) rates of this procedure are low in centers with expertise, despite the high-risk population. Long-term follow-up is needed to ensure adequate protein, calorie, vitamin, and mineral nutrition. Supplemental vitamin B_{12}, iron, and calcium are routinely added to standard multivitamins. Almost all of the weight loss that occurs happens during the first 1 to 2 years. Long-term (>5 year) success rates are outstanding in good programs. Virtually all patients with successful weight loss experience a dramatic improvement in the medical complications of obesity. For these reasons, bariatric surgery has become an important tool in the treatment of severe, medically complicated obesity.

PREVENTION. The dramatic increase in the prevalence of obesity over the past few decades strongly suggests that preventative strategies will become more important as time goes on. Public health approaches that emphasize education have been almost uniformly unsuccessful at preventing weight gain or producing weight loss. Public health strategies that virtually impose behavior change are more successful in this regard. Unless widespread efforts are made to address the problem of obesity, it is likely that its prevalence and complications will become an ever-increasing health burden in the United States.

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chromogranin A measurements can then be used to gauge tumor response to treatment.

In patients with malignant pheochromocytoma, α- and β-adrenergic blockade with phenoxybenzamine and propranolol remains the mainstay of management of the symptoms and signs of catecholamine excess. If catecholamine effects are not controlled, the tyrosine hydroxylase inhibitor α-methylparatyrosine can be effective at 0.25 to 1.0 g four times daily.

Metastases tend to be slow-growing, and the natural history of malignant pheochromocytoma is variable; the 5-year survival rate is less than 50%. Common sites of metastasis are the retroperitoneum, skeleton (bone), lymph nodes, and liver. Periodic surgical debulking may help control symptoms. The response to chemotherapy has generally been disappointing, but the combination of vincristine, cyclophosphamide, and dacarbazine shows promise in many patients. Skeletal metastases show some response to irradiation, although the neoplasm is not particularly susceptible to radiation therapy. High-dose (approximately 500 mCi cumulative dose) repeated radiation therapy with intravenous [^{131}I]-MIBG remains experimental but is of value in some patients.

CATECHOLAMINE DEFICIENCY DISEASE STATES

Loss of even both adrenal glands seldom produces a catecholamine deficiency state. In diabetic patients receiving insulin, the usual counter-regulatory response to hypoglycemia involves the actions of epinephrine and glucagon to trigger hepatic glycogenolysis. In diabetic patients who also have autonomic neuropathy, deficient epinephrine release during hypoglycemia coupled with deficient glucagon responses may result in impairment of the usual counter-regulatory response to hypoglycemia and prolong its duration.

Several individuals have been described with hereditary deficiency of dopamine β-hydroxylase; such individuals have greatly diminished or undetectable norepinephrine and epinephrine levels in blood, urine, and cerebrospinal fluid. The initial features of this lifelong syndrome include severe orthostatic hypotension, ptosis, nasal stuffiness, hyperextensible joints, and retrograde ejaculation. The diagnosis is made in patients with severe orthostatic hypotension, a plasma norepinephrine/dopamine ratio of less than 1, and undetectable plasma dopamine β-hydroxylase enzymatic activity and immunoreactivity. During sympathoadrenal activation in these subjects, increments in efferent sympathetic nerve traffic occur, but sympathetic axons release the precursor dopamine instead of norepinephrine, perhaps compounding the hypotension.

THE INCIDENTAL ADRENAL MASS (OR "INCIDENTALOMA")

About 2% of all abdominal CT scans, as well as 9% of autopsies, incidentally discover minimal adrenal gland abnormalities. Rarely do these lesions require further attention.

Occasionally, the appearance of an adrenal mass on CT or MRI scan is sufficiently characteristic for a firm diagnosis; an example is adrenal myelolipoma, a benign accumulation of bone marrow elements in an otherwise normally functioning adrenal gland with a characteristic fat-density image on CT or MRI scan. Myelolipoma requires no treatment.

If an adrenal mass is larger than 4 cm in span, its chance of malignancy (especially adrenocortical carcinoma) increases, and such masses should be resected unless they have a clearly benign appearance (such as myelolipoma) on CT or MRI scan. In smaller lesions, adrenal carcinoma is unlikely unless other signs or symptoms of adrenocortical hormone excess are apparent. Incidental masses smaller than 4 to 6 cm in span are monitored by periodic CT scanning. In subjects with known metastatic carcinoma, adrenal abnormalities are likely to be adrenal metastases. In subjects with recent major abdominal trauma, adrenal abnormalities probably represent hemorrhage and should resolve with time.

Because not all pheochromocytomas manifest hypertension at all times, all patients with incidental adrenal masses should be screened for pheochromocytoma with a 24-hour urine collection for catecholamine metabolites.

Virtually all patients with aldosterone-producing adrenal adenoma have hypertension, although hypokalemia may not be constant. Screening for primary aldosteronism can be readily accomplished with an ambulatory morning plasma aldosterone concentration to plasma renin activity ratio (PAC [ng/dL]/PRA [ng/mL/hour] ratio). A PAC/PRA ratio of greater than 20 and PAC greater than 15 ng/dL constitutes a positive screening test result.

Whereas frank Cushing's disease is heralded by classic signs or symptoms, preclinical Cushing's disease may lack the typical signs and symptoms of hypercortisolism. In either case, the diagnosis is made by giving 1 mg of oral dexamethasone at 11 PM and sampling serum cortisol the next morning at 8 AM; a cortisol value of less than 5 μg/dL is normal.

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242 DIABETES MELLITUS

Robert S. Sherwin

Overview

Diabetes mellitus is a chronic disorder characterized by the impaired metabolism of glucose and other energy-yielding fuels as well as by the late development of vascular and neuropathic complications. Diabetes comprises of a group of disorders involving distinct pathogenic mechanisms, for which hyperglycemia is the common denominator. Regardless of its cause, the disease is associated with a common hormonal defect, namely, insulin deficiency, which may be total, partial, or relative when viewed in the context of coexisting insulin resistance. Lack of insulin *effect* plays a primary role in the metabolic derangements linked to diabetes, and hyperglycemia in turn plays an important role in disease-related complications.

In 1998, the United States Centers for Disease Control and Prevention estimated that 16 million Americans (or nearly 6% of the U.S. population) fulfilled the diagnostic criteria for diabetes mellitus; more than one third of these cases were thought to be undiagnosed. The number of affected patients continues to rise as the 21st century begins, with current estimates exceeding 800,000 new cases per year. Diabetes is the fourth most common reason for patient contact with an American physician, accounting for approximately 12% of U.S. health care dollars and total annual costs exceeding 100 billion dollars. Worldwide, diabetes affects more than 135 million people; this figure is projected to reach 300 million cases by 2025. Unfortunately, the rate of growth of diabetes is largest in developing nations, where barriers exist to proper diagnosis and treatment.

Diabetes is a leading cause of both mortality and early disability; in the United States, it is the leading cause of blindness among working-age adults, of end-stage renal disease, and of nontraumatic limb amputations. Diabetes increases the risk of cardiac, cerebral, and peripheral vascular disease two- to seven-fold and in the obstetric setting is a major contributor to neonatal morbidity and mortality. On the bright side, a growing body of evidence suggests that most (if not all) of the debilitating complications of diabetes (Fig. 242–1) can be prevented or delayed by the prospective treatment of hyperglycemia and other cardiovascular risk factors. When treating diabetes, the timing of

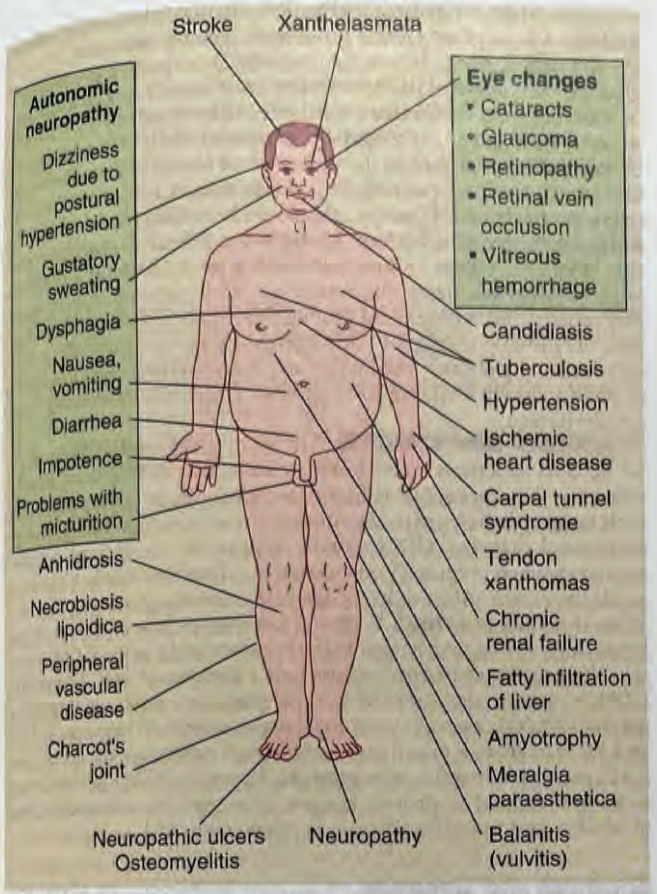

FIGURE 242–1 • Long-term complications of diabetes mellitus. (From Forbes CD, Jackson WF: Color Atlas and Text of Clinical Medicine, 3rd ed. London, Mosby, 2003, with permission.)

Table 242–1 • CLASSIFICATION OF DIABETES MELLITUS

ESTABLISHED DIABETES MELLITUS

I. Type 1 diabetes, formerly known as insulin-dependent diabetes mellitus (IDDM) or "juvenile-onset diabetes" (primarily due to β-cell destruction, usually leading to absolute insulin deficiency)
   A. Immune mediated
   B. Idiopathic
II. Type 2 diabetes, formerly known as non-insulin-dependent diabetes (NIDDM) or "adult-onset diabetes" (may range from predominantly insulin resistance with relative insulin deficiency to predominantly secretory defect with insulin resistance)
III. Other specific types
   A. Genetic defects of β-cell function (e.g., maturity-onset diabetes of the young [MODY] types 1–6 and point mutations in mitochondrial DNA)
   B. Genetic defects in insulin action (e.g., type A insulin resistance, leprechaunism, Rabson-Mendenhall syndrome, lipoatrophic diabetes)
   C. Disease of the exocrine pancreas (e.g., pancreatitis, trauma, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy)
   D. Endocrinopathies (e.g., acromegaly, Cushing's syndrome, hyperthyroidism, pheochromocytoma, glucagonoma, somatostinoma, aldosteronoma)
   E. Drug- or chemical-induced (e.g., vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon)
   F. Infections (e.g., congenital rubella, cytomegalovirus)
   G. Uncommon forms of immune-mediated diabetes (e.g., "stiff-man" syndrome, anti-insulin receptor antibodies)
   H. Other genetic syndromes (e.g., Down sydrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's sydrome, Friedrich's ataxia, Huntington's disease, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome)
IV. Gestational diabetes mellitus

RISK CATEGORIES FOR DIABETES MELLITUS

I. Impaired fasting glucose (IFG)
II. Impaired glucose tolerance (IGT)

therapy is crucial; clinical outcomes depend critically on early recognition and treatment of the disease.

Classification

The newly revised American Diabetes Association (ADA) classification scheme for diabetes mellitus is summarized in Table 242–1. Clinical diabetes is divided into four general subclasses, including (1) type 1, primarily caused by autoimmune pancreatic β-cell destruction and characterized by absolute insulin deficiency; (2) type 2, characterized by insulin resistance and relative insulin deficiency; (3) "other" specific types of diabetes, associated with identifiable clinical conditions or syndromes; and (4) gestational diabetes mellitus. In addition to these clinical categories, two "risk conditions"—*impaired glucose tolerance (IGT)* and *impaired fasting glucose (IFG)*—have been defined to describe metabolic states in between normal glucose homeostasis and overt diabetes. Both IGT and IFG significantly increase the future risk of developing diabetes mellitus, and in many cases are part of the disease's natural history. It should also be noted here that patients with any form of diabetes may require insulin therapy; for this reason, the previously used terms "insulin-dependent" (for type 1) and "non-insulin-dependent" (for type 2) diabetes have been eliminated.

TYPE 1 DIABETES MELLITUS. Patients with type 1 diabetes mellitus have little or no insulin secretory capacity and depend on exogenous insulin to prevent metabolic decompensation and death. Classically, symptoms appear abruptly (i.e., over days or weeks) in previously healthy, nonobese children or young adults; in older patients, however, the disease may manifest more gradually. At the time of initial evaluation, most type 1 diabetic patients are ill and symptomatic, most commonly presenting with polyuria, polydipsia, polyphagia, and weight loss; such patients may also present with ketoacidosis. Type 1 diabetes is believed to have a prolonged asymptomatic preclinical phase (often lasting years), during which pancreatic β cells are gradually destroyed by an autoimmune attack influenced by HLA and other genetic factors, as well as by the environment (Fig. 242–2). In some patients, an acute illness may speed the transition from the preclinical phase to clinical disease. Initially, most type 1 patients require high-dose insulin therapy to restore a disordered metabolism. A so-called "honeymoon period" (lasting weeks or months) may follow, however, during which small doses of insulin are needed due to partial recovery of β-cell function and reversal of the insulin resistance caused by acute illness. Thereafter, insulin secretory capacity is gradually lost; this process may take several years. That type 1 diabetes is an autoimmune disease is supported by its association with specific immune response (HLA) genes and by the presence of autoantibodies to islet cells and their constituents (e.g., insulin, glutamic acid decarboxylase). Type 1 diabetes accounts for less than 10% of cases of diabetes in the United States.

TYPE 2 DIABETES MELLITUS. Type 2 accounts for over 90% of cases of clinical diabetes. Patients with type 2 disease retain some endogenous insulin secretory capacity; however, their insulin levels are low relative to their ambient glucose levels and magnitude of insulin resistance. Type 2 patients are not dependent on insulin for immediate survival, and ketosis rarely develops, except under conditions of great physical stress. Nevertheless, many of these patients do require insulin therapy for proper glycemic control. Although found with increasing frequency in adolescents, type 2 diabetes is usually associated with advancing age; most cases are diagnosed after age 45. Type 2 diabetes has a high rate of genetic penetrance unrelated to HLA genes and is associated with a high-fat diet, obesity, and/or a lack of physical activity. The clinical features of type 2 diabetes can be quite insidious; classic symptoms may be mild (fatigue, weakness, dizziness, blurred vision, and other nonspecific complaints may dominate the clinical picture) or may be tolerated for many years before a patient seeks medical attention. Moreover, if the degree of hyperglycemia is insufficient to produce symptoms, the diagnosis may be made only after the development of vascular or neuropathic complications.

OTHER SPECIFIC TYPES OF DIABETES. This category encompasses a wide variety of diabetic syndromes attributed to a specific disease, drug,

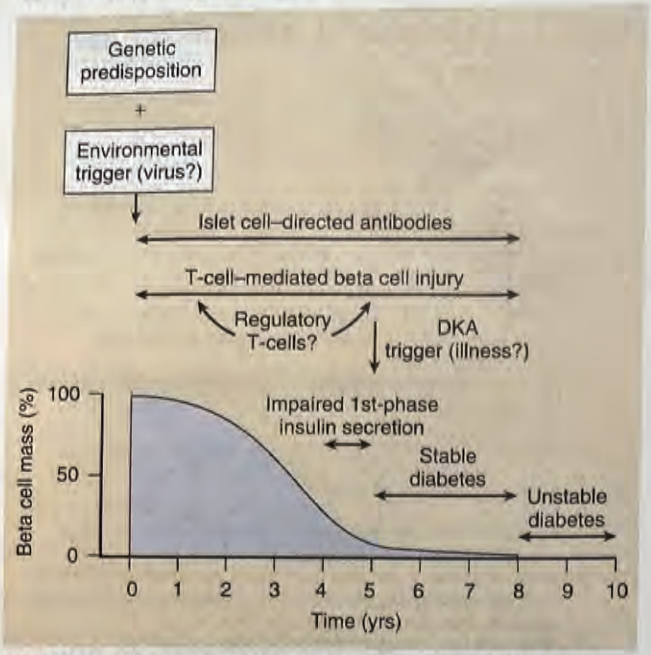

FIGURE 242–2 • A summary of the sequence of events that lead to pancreatic β-cell loss, and ultimately to the clinical appearance of type 1 diabetes. DKA = diabetic ketoacidosis.

or condition (see Table 242–1). Categories include genetic defects of β-cell function or insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced diabetes, infections, and other immune-mediated and genetic syndromes associated with diabetes mellitus.

Maturity-onset diabetes of the young (MODY), formerly classified as a subtype of type 2 diabetes, has now been more accurately described as a consequence of genetic research. Clinically, patients with MODY generally present in adolescence or young adulthood; unlike patients with classic type 2 diabetes, they are usually nonobese, normotensive, and normolipidemic at the time of diagnosis. MODY is a heterogeneous disorder encompassing several monogenic defects of β-cell function, with autosomal dominant inheritance and penetrance exceeding 80%. Mutations at several genetic loci have been identified. The most common form—MODY type 3—is associated with a mutation of hepatocyte nuclear factor 1a (HNF-1a), a gene transcription factor encoded on chromosome 12. MODY type 2 patients share a mutation in the gene encoding glucokinase, the key enzyme responsible for the phosphorylation of glucose within the β cell and the liver. A variety of glucokinase mutations have been identified in different families, each capable of interfering with the transduction of the glucose signal to the β cell. Other described forms of MODY are shown in Table 242–2; the existence of additional forms of MODY is suggested by the presence of patient clusters with similar clinical findings whose genetic basis for disease remains unknown.

Severe illness (e.g., burns, trauma, sepsis) can provoke stress hyperglycemia as a result of the hypersecretion of insulin antagonistic hormones (e.g., catecholamines, cortisol). Although this may represent the unmasking of underlying diabetes, the metabolic disturbance may be self-limited and should therefore not be formally classified as diabetes until the precipitating illness has resolved. It should also be emphasized that while most patients can be readily classified on clinical grounds, a small subgroup of patients are difficult to classify because they display features common to both type 1 and type 2 diabetes. Such patients are classically nonobese, with reduced insulin secretory capacity but little tendency for ketosis. Many of these "in-between" patients initially respond to oral agents; however, nearly all of them will eventually require insulin therapy. Many of these patients appear to have a slowly evolving form of type 1 diabetes; others defy easy categorization.

GESTATIONAL DIABETES MELLITUS. The term *gestational diabetes mellitus* (GDM) describes a condition in women with impaired glucose tolerance that appears or is first detected *during* pregnancy. Women with known diabetes prior to conception are *not* classified as having gestational diabetes. GDM usually appears in the second or third trimester, when pregnancy-associated insulin antagonistic hormones reach their peak. After delivery, glucose tolerance generally (but not always) reverts to normal. Within 5 to 10 years, however, type 2 diabetes develops in nearly one half of women with prior GDM; occasionally, pregnancy can precipitate type 1 diabetes as well. As a whole, GDM occurs in about 4% of U.S. pregnancies, producing approximately 135,000 cases per year; local prevalence rates may rise as high as 14% in high-risk populations. Although patients with GDM generally present with mild, asymptomatic hyperglycemia, rigorous treatment is indicated to protect against hyperglycemia-associated fetal morbidity and mortality. Insulin is often required.

Diagnosis and Screening

The diagnosis of diabetes mellitus is straightforward when classic symptoms of polyuria, polydipsia, and unexplained weight loss are present. In these cases, a random plasma glucose measurement of 200 mg/dL or greater is sufficient to clinch the diagnosis; confirmatory testing is unwarranted and may delay treatment. Although glycosuria is strongly suggestive of diabetes, urine test results should never be used exclusively to diagnose diabetes, since an altered renal threshold for glucose can produce similar findings. If suspected diabetes is not confirmed through random glucose determination, additional diagnostic testing should be performed.

An 8-hour (overnight) fasting plasma glucose measurement is most convenient; diabetes is established if fasting glucose levels are 126 mg/dL or greater on two separate occasions. Alternatively, a 75 g oral glucose tolerance test (oGTT) may be employed. The oGTT should be performed after an overnight fast, using a glucose load containing 75 g of anhydrous glucose dissolved in water; 2-hour postload glucose levels of 200 mg/dL or greater confirm the presence of diabetes. An important note about the oGTT: while able to detect diabetes in its earliest stage, this test should be performed under controlled conditions to ensure its accuracy. Common factors that nonspecifically

Table 242–2 • CLASSIFICATION OF CURRENTLY RECOGNIZED GENETIC DEFECTS OF β-CELL FUNCTION: MATURITY-ONSET DIABETES OF THE YOUNG (MODY)

MODY	CHROMOSOME	DEFECTIVE GENE PRODUCT	MOLECULAR DEFECT	MOST COMMON TREATMENT
1	20q	HNF-4α	β-Cell mass, insulin secretion	OHA, insulin
2	7p	Glucokinase	Glucose phosphorylation	Diet and exercise
3	12q	HNF-1α	β-Cell mass, insulin secretion	OHA, insulin
4	13q	IPF-1 (PDX-1)	β-Cell development and function	OHA, insulin
5	17cen-q	HNF-1β	β-Cell mass, insulin secretion	Insulin
6	2q	Neuro D1 (BETA2)	β-Cell development and function	Insulin

HNF = hepatocyte nuclear factor; IPF = insulin promoter factor; Neuro D1 = neurogenic differentiation factor 1; OHA = oral hypoglycemic agent.

Adapted from Fajans SS, Bell GI, Polonsky KS: Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001;345:971–980.

deteriorate the oGTT include (1) carbohydrate restriction (<150 g for 3 days), (2) bed rest or severe inactivity, (3) medical or surgical stress, (4) drugs (e.g., thiazides, β-blockers, glucocorticoids, or phenytoin), (5) smoking, and (6) anxiety from repeated needlesticks. As a result, the oGTT should not be performed in acutely ill patients, and patients taking the oGTT should ideally stop smoking and consume a liberal carbohydrate diet for at least 3 days prior to testing. The current American Diabetes Association criteria for the diagnosis of diabetes mellitus are shown below; in the absence of unequivocal hyperglycemia with acute metabolic decompensation, each criterion used should be confirmed by repeat testing on a separate occasion.

1. Classic symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) *PLUS* random glucose concentration of 200 mg/dL or greater (≥11.1 mmol/L) *OR*
2. Fasting (≥8-hour) plasma glucose concentration of 126 mg/dL or greater (≥ 7.0 mmol/L) *OR*
3. 2-hour postload glucose concentration of 200 mg/dL or greater (≥11.1 mmol/L) during a 75 g oGTT

In recent years, increasing emphasis has been placed on two "risk categories" for diabetes, IFG and IGT. Since both conditions are associated with an increased risk of developing diabetes and subsequent vascular disease, all patients with IFG or IGT should be treated with diet and exercise and should be screened annually for progression to diabetes. The recent report of the NIH-funded Diabetes Prevention Program as well as studies from Finland and China have demonstrated that modest changes in life style sharply reduced the development of type 2 diabetes in patients with IGT. As detailed earlier, diabetes mellitus is established if fasting glucose levels are 126 mg/dL or greater; however, a fasting glucose concentration of 109 mg/dL, not 125 mg/dL, has been designated as the upper limit of normal. While somewhat arbitrary, this level was chosen because it approximates the level above which acute-phase insulin secretion is suppressed in response to intravenous glucose. More importantly, fasting glucose levels above 109 mg/dL are associated with an increased risk of developing diabetes. Patients with fasting glucose levels between 110 and 125 mg/dL are classified as having IFG (Table 242–3). Because individuals with IFG may exhibit severe postprandial hyperglycemia, a 75 g oGTT should be performed in all such patients to rule out diabetes. During the 75 g oGTT, 2-hour postload glucose concentrations of 200 mg/dL or greater are diagnostic of diabetes, whereas patients with levels between 140 and 199 mg/dL are defined as having IGT. Table 242–3 summarizes the diagnosis of IFG, IGT, and overt diabetes mellitus.

Because patients with diabetes may harbor the disease for many years before symptoms are appreciated, the ADA has endorsed the screening of "high-risk" individuals at 3-year intervals (Table 242–4). By current ADA criteria, "high-risk" patients include those with a personal history of IFG, IGT, GDM, obesity, hypertension, or dyslipidemia. Patients in high-risk ethnic groups and patients with first-degree relatives with diabetes also qualify for screening. In most cases, a fasting plasma glucose level is the screening test of choice; however, the oGTT has the distinct advantage of detecting patients with IGT.

Table 242–3 • DIAGNOSTIC CATEGORIES: IMPAIRED FASTING GLUCOSE, IMPAIRED GLUCOSE TOLERANCE, AND DIABETES MELLITUS*

	2-HOUR (75-G) OGTT RESULT		
	<140 mg/dL	140–199 mg/dL	>22 mg/dL
FASTING PLASMA GLUCOSE			
<110 mg/dL	Normal	IGT	DM
110–125 mg/dL	IFG	IGT *and* IFG	DM
≥126 mg/dL	DM	DM	DM

*These diagnostic categories are based on the combined results of a fasting plasma glucose level and a 2-hour, 75-g oral glucose tolerance test. Note that a confirmed random plasma glucose level of ≥200 mg/dL in the appropriate clinical setting is diagnostic of diabetes and precludes the need for further testing.

DM = diabetes mellitus; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; oGTT = oral glucose tolerance test.

Table 242–4 • CRITERIA FOR DIABETES SCREENING IN ASYMPTOMATIC INDIVIDUALS*

1. Testing for diabetes should be considered in all individuals at age 45 years and older and, if results are normal, it should be repeated at 3-year intervals.
2. Testing should be considered at a younger age or be carried out more frequently in individuals who
   - 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 (e.g., African-American, Hispanic American, Native American, Asian American, Pacific Islander)
   - Have delivered a baby weighing >9 pounds or have been diagnosed with gestational diabetes mellitus
   - Have systemic hypertension (blood pressure >140/90)
   - Have a high-density lipoprotein cholesterol level <35 mg/dL and/or a triglyceride level >250 mg/dL
   - On previous testing, had impaired glucose tolerance or impaired fasting glucose

*A fasting plasma glucose (FPG) or an oral glucose tolerance test (OGTT) can be used for diagnosis. In most clinical settings, the FPG is preferred because of ease of administration, convenience, acceptability to patients, and lower cost.

Adapted from Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2000;23(Suppl 1):S4–S19.

GESTATIONAL DIABETES MELLITUS. Since even mild glucose elevations can have serious adverse effects on a developing fetus, an aggressive screening approach is recommended during pregnancy. Women with a high clinical risk of gestational diabetes (personal history of GDM, obesity, glycosuria, or a strong family history of diabetes) should undergo screening as soon as possible after conception; in these patients, screening *prior* to pregnancy is preferred if possible. At 24 to 28 weeks of gestation, screening is recommended for *all* pregnant women, except those in the lowest risk category who meet *all* of the following clinical characteristics:

- Age less than 25 years
- Weight normal before pregnancy
- Member of an ethnic group with a low risk of GDM (e.g., European)
- No known diabetes in first-degree relatives
- No history of abnormal glucose tolerance
- No history of poor obstetric outcome

In pregnant women, a casual plasma glucose level of 200 mg/dL or greater or a confirmed fasting plasma glucose level of 126 mg/dL or greater establishes the diagnosis of GDM and precludes the need for a glucose challenge. In the absence of obvious hyperglycemia, a screening 1-hour 50 g oGTT should be performed between 24 and 28 weeks of gestation. If the fasting glucose level is 105 mg/dL or greater or the 1-hour postload value is 140 mg/dL or greater, a diagnostic 100 g oGTT is indicated. Gestational diabetes is then diagnosed if two or more values equal or exceed the upper limits of normal: fasting, 95 mg/dL; 1-hour, 180 mg/dL; 2-hour, 155 mg/dL; and 3-hour, 140 mg/dL. To save time and effort, proceeding directly to the 100 g diagnostic oGTT is an acceptable alternative.

Prevalence/Epidemiology

TYPE 1 DIABETES. Prevalence rates for type 1 diabetes are relatively accurate, since these patients invariably become symptomatic; current estimates for the United States hover between 0.3 and 0.4%. Type 1 diabetes is more prevalent in Finland, Scandinavia, and Scotland, less prevalent in Southern Europe and the Middle East, and uncommon in Asian nations. The annual incidence appears to have risen in the last half-century, which could imply the introduction of an unidentified environmental factor. Prevalence rates are strikingly different among ethnic groups living in the same geographic region, likely due to genetic differences in susceptibility to the disease.

Recent recognition that type 1 diabetes has a protracted preclinical phase has shed new light on some epidemiologic characteristics of the disease. Type 1 diabetes has an increased incidence in the winter months and may be associated with specific viral epidemics. These

observations may in part be explained by the superimposition of illness-provoked insulin resistance in patients with marginal β-cell function. Similarly, the common appearance of type 1 diabetes during puberty may also be attributed to insulin resistance; even under normal circumstances, puberty is accompanied by impaired insulin-stimulated glucose metabolism. New methods for tracking islet-directed autoimmunity have led to a reappraisal of the age at which type 1 diabetes first appears. Although the age-specific incidence rises progressively from infancy to puberty and then declines, incidence rates persist at lower levels for many decades; in fact, about 30% of patients are diagnosed after the age of 20 years. In the later-onset patients, the clinical syndrome tends to evolve more slowly; in addition, islet-directed antibody titers may be lower, and HLA types may be different from those of younger patients. As a result, type 2 diabetes mellitus is initially misdiagnosed in many of these patients.

TYPE 2 DIABETES. Systematic screening for asymptomatic diabetes mellitus is generally limited to high-risk populations, rendering broader prevalence estimates imprecise. Total U.S. prevalence has been estimated at 6% but likely exceeds 10 or 15% in persons older than 50 years of age; one third of these cases are thought to be undiagnosed. Type 2 diabetes is more common in Native Americans, Hispanic Americans, and African Americans than in people of European heritage; these patients also typically present at an earlier age. Prevalence rates also vary worldwide, where type 2 diabetes has a propensity for Asiatic Indians, Polynesians/Micronesians, and Latin Americans. Interestingly, African blacks, Australian Aborigines, Asians, and Pacific Islanders all have an increased risk of diabetes after emigration to the United States; this may be attributable to a genetically determined inability to metabolically adapt to "Western" behavior patterns, such as reduced physical activity and a high-fat, high-calorie diet.

Although relatively little is known about the specific genetic abnormalities associated with type 2 diabetes, the personal factors promoting disease expression are well established. Increased age, reduced physical activity, and especially obesity promote the expression of disease in genetically susceptible persons. The severity and duration of obesity contribute significantly to diabetes risk; patients with high waist-hip ratios (i.e., central or upper body obesity) are also more prone to the disease. Family history is also very important, since type 2 diabetes occurs more frequently in persons with diabetic parents or siblings. Identical twin concordance rates approach 100%; in these cases, affected twins will even develop diabetes at a similar age.

IMPAIRED FASTING GLUCOSE AND IMPAIRED GLUCOSE TOLERANCE. Precise statistical data regarding the prevalence of these diagnostic categories are lacking. In the United States, it is estimated that about 10–12 million people have impaired fasting glucose levels, while about 20 million have impaired glucose tolerance. The diagnoses often overlap as well: approximately 37% of patients with IFG also have IGT, and approximately 24% of patients with IGT also have IFG. Owing to the insidious nature of both conditions, precise rates of progression to overt diabetes are difficult to establish; current estimates approach 5 to 8% per year for each condition, with even higher rates if both conditions are present. In general, IGT and IFG have similar capacity to predict the future development of diabetes. IGT is also an independent risk factor for cardiovascular complications.

Pathophysiology

INSULIN SECRETION AND ACTION. The gene coding for human insulin is located on the short arm of chromosome 11. Insulin is initially synthesized in pancreatic β cells as *proinsulin*, a single-chain, 86 amino acid polypeptide. Subsequent cleavage of proinsulin removes a connecting strand (*C-peptide*) to form the smaller, double-chain insulin molecule, which contains 51 amino acid residues. Both insulin and the C-peptide remnant are packaged in membrane-bound storage granules; stimulation of insulin secretion results in the discharge of equimolar amounts of insulin and C-peptide (and a small amount of proinsulin) into the portal circulation. Although insulin is heavily metabolized during its first pass through the liver, the C-peptide fragment largely escapes hepatic metabolism; as a result, peripheral C-peptide levels provide a more precise marker of endogenous insulin secretion.

Glucose concentration is the key regulator of insulin secretion. To activate secretion, a glucose molecule must first be transported by a protein (GLUT 2) into the β cell, phosphorylated by the enzyme glucokinase, and metabolized. The precise triggering process is poorly understood but probably involves activation of signal transduction pathways and mitochondrial signals, closure of adenosine triphosphate–sensitive potassium channels, and calcium entry into the cytoplasm of the β cell. Normally, when blood glucose rises even slightly above fasting levels, β cells secrete insulin, initially from preformed (stored) insulin and later from de novo insulin synthesis. The magnitude of the insulin response is determined by the amount of glucose available as well as by the mode of glucose entry; compared with intravenous administration, higher insulin levels are produced when glucose is given orally because of the simultaneous release of gut peptides (e.g., glucagon-like peptide 1, gastric inhibitory polypeptide), which amplify the insulin response. Other insulin secretagogues include amino acids (e.g., leucine), vagal stimulation, sulfonylureas, repaglinide, and nateglinide (see later). Once secreted into the portal vein, 50% or more of insulin is removed by first pass through the liver. The consequence of this hepatic metabolism is that portal vein insulin levels are at least two- to four-fold higher than levels in the peripheral circulation. This point has clinical relevance with regard to insulin therapy; whereas insulin secreted by pancreatic β cells directly enters the portal circulation, peripherally administered insulin does not raise portal insulin levels and therefore may be less efficient in inducing hepatic effects.

Insulin acts on its target tissues (liver, muscle, and fat, primarily) through a specific insulin receptor, which is a heterodimer containing two α- and two β-chains linked by disulfide bridges. The α-subunits of the receptor reside on the extracellular surface and are the sites of insulin binding. The β-subunits span the membrane and can be phosphorylated on serine, threonine, and tyrosine residues on the cytoplasmic face. The intrinsic protein tyrosine kinase activity of the β-subunit is essential for the function of the insulin receptor. Rapid receptor autophosphorylation and tyrosine phosphorylation of cellular substrates are important early steps in insulin action. Thereafter, a series of phosphorylation and dephosphorylation reactions are triggered that produce insulin's ultimate effects. A variety of post-receptor signal transduction pathways are activated by insulin, including PI3 (phosphatidylinositol 3′) kinase, an enzyme whose product appears to be critical for the eventual translocation of glucose transport proteins (GLUT 4) to the cell surface to facilitate glucose uptake.

A number of so-called "counter-regulatory" hormones oppose the metabolic actions of insulin, including glucagon, growth hormone, cortisol, and catecholamines. Among these, glucagon (and to a lesser extent, growth hormone) plays the most important role in the development of diabetes. Glucagon is normally secreted by pancreatic α cells in response to hypoglycemia, amino acids, and activation of the autonomic nervous system. Its chief effects are on the liver, where it stimulates glycogenolysis, gluconeogenesis, and ketogenesis via cyclic adenosine monophosphate–dependent mechanisms. Glucagon release is normally inhibited by hyperglycemia and hyperinsulinemia; however, in both types of diabetes, glucagon levels are absolutely or relatively *elevated* despite the presence of hyperglycemia. Growth hormone secretion by the anterior pituitary gland is also inappropriately increased in type 1 diabetes, a result (at least in part) of the body's attempt to overcome a defect in insulin-like growth factor type 1 generation caused by insulin deficiency. The major metabolic actions of growth hormone are on peripheral tissues, where it acts to promote lipolysis and inhibit glucose consumption. In type 1 diabetic patients with reduced portal insulin levels, growth hormone is also capable of stimulating hepatic glucose production.

METABOLIC EFFECTS OF INSULIN. Insulin deficiency—be it relative or absolute—plays a pivotal role in the pathophysiology of diabetes mellitus. The effects of insulin lack are best appreciated by first examining the normal role of insulin in fuel homeostasis.

Fasted State. After an overnight fast, low basal insulin levels result in diminished glucose uptake in peripheral insulin-sensitive tissues (e.g., muscle and fat). In the fasted state, most glucose uptake occurs in non-insulin-sensitive tissues, primarily the brain, which, because of its inability to use free fatty acids, is critically dependent on a constant supply of glucose for oxidative metabolism. Maintenance of stable blood glucose levels is achieved through the release of glucose by the liver (and to a small extent, by the kidney); production rates of 7 to 10 g per hour (~2 mg/kg/min) match those of the consuming tissues. The hepatic processes involved are glycogenolysis and gluconeogenesis; both play a significant role, and both depend critically on the balance between insulin and glucagon in the portal circulation. Reduced portal insulin levels decrease glycogen synthesis, which allows glucagon's stimulatory effect on glycogenolysis to prevail. Glucagon predominance also stimulates gluconeogenesis, while concurrent low insulin

levels promote the peripheral mobilization of glucose precursors (amino acids, lactate, pyruvate, glycerol) and fuels (free fatty acids) for gluconeogenesis.

Fed State. Ingestion of a large glucose load triggers multiple homeostatic mechanisms to minimize glucose excursions, including (1) suppression of endogenous glucose production, (2) stimulation of hepatic glucose uptake, and (3) acceleration of glucose uptake by peripheral tissues, predominantly muscle. Each of these mechanisms depends principally on insulin. In the liver, meal-stimulated insulin levels rapidly suppress glucose production. At least 30% of ingested glucose is deposited directly in the liver, via glycogen synthesis and storage; concurrently, hepatic triglyceride synthesis increases. Peripherally, insulin-stimulated glucose transport across the plasmalemma of both adipose and muscle tissue is attributable to the recruitment of glucose transport proteins (i.e., GLUT 4) from the cytosolic compartment to the plasma membrane. In muscle, glucose may then be metabolized, or it may be converted to glycogen for storage. In adipose tissue, glucose is used primarily for the formation of α-glycerophosphate, which is necessary for the esterification of free fatty acids to form triglycerides for storage in adipose tissue.

The scenario described—the ingestion of large quantities of pure glucose—is not representative of conditions during ordinary meals. If the quantity of carbohydrate consumed and resulting insulin response are small, glucose homeostasis is maintained largely by reduced hepatic glucose production rather than by increased glucose uptake, because glucose production is much more sensitive than glucose uptake to the effects of small changes in insulin secretion. The rise in insulin that accompanies the consumption of mixed meals also facilitates protein and fat storage. Because muscle is in negative nitrogen balance in the fasting state, repletion of muscle nitrogen depends on the net uptake of amino acids in response to protein feeding. In muscle, insulin acts to promote positive nitrogen balance by facilitating amino acid uptake, by inhibiting the breakdown of protein, and (to a lesser extent) by stimulating new protein synthesis. In adipose tissue, the action of insulin accelerates triglyceride incorporation by stimulating lipoprotein lipase, while simultaneously inhibiting the hormone-sensitive lipase that catalyzes the hydrolysis of stored triglycerides. In adipose tissue, the net effect of insulin is to promote the synthesis and storage of triglycerides.

METABOLIC DEFECTS IN DIABETES. In both type 1 and type 2 diabetes, fasting hyperglycemia is accompanied by an inappropriate increase in hepatic glucose production; this effect is magnified in type 1 diabetes due to absolute portal insulin deficiency. In addition, total body glucose uptake is generally increased in diabetes, largely due to mass action induced by hyperglycemia. Increased hepatic glucose production in both types of diabetes is due mostly to accelerated gluconeogenesis; the loss of insulin's restraining effect on the α cell also leads to a relative increase in portal glucagon levels, resulting in increased uptake and conversion of glycogenic substrates to glucose within the liver. Insulin deficiency also leads to the hypersecretion of growth hormone, which further accentuates glucose overproduction. In the extreme situation of total insulin lack, excessive counter-regulatory hormone release further stimulates gluconeogenesis, while blocking compensatory increases in glucose disposal. The clinical correlate is profound hyperglycemia and glycosuria (Fig. 242–3).

Diabetes is also characterized by marked postprandial hyperglycemia. In type 2 diabetes, delayed insulin secretion and hepatic insulin resistance join forces to impair both suppression of hepatic glucose production and the liver's ability to store glucose as glycogen. Hyperglycemia ensues, even though insulin levels may eventually rise to levels above those seen in nondiabetic individuals (insulin secretion remains deficient relative to the prevailing glucose level), because insulin resistance reduces the capacity of myocytes to extract and store the excess glucose released from the liver. Under normal circumstances, muscles show increased levels of glucose-6-phosphate after sensing insulin; this rise is markedly attenuated in diabetes, which implies that the block in glycogen synthesis precedes glucose-6-phosphate formation, and thus is mediated at the level of either glucose transport (by GLUT 4) or the conversion of glucose to glucose-6-phosphate (by hexokinase). These defects are more pronounced in patients with severe hyperglycemia, in whom insulin secretion is further reduced. Type 1 patients show the most marked and prolonged elevations in blood glucose after ingestion of carbohydrate. These individuals have low portal vein insulin levels, which cannot be reversed by subcutaneous insulin therapy. Consequently, during hyperglycemia, the liver fails to arrest glucose production and fails to

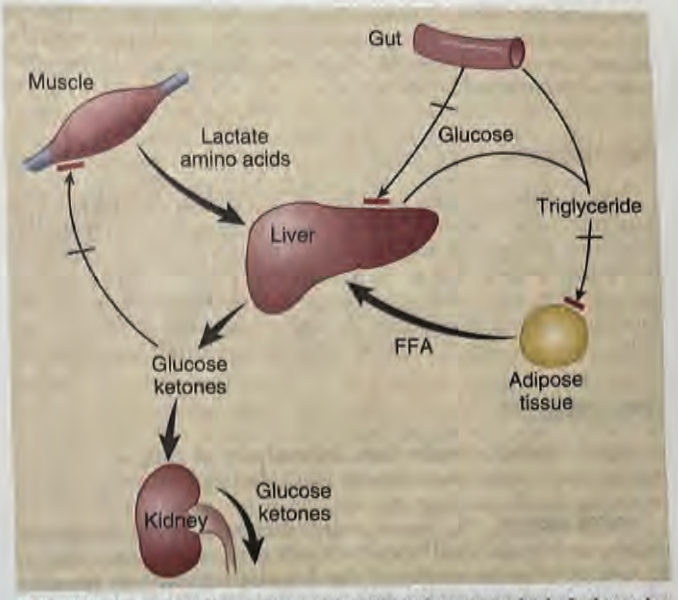

FIGURE 242–3 • The effects of severe insulin deficiency on body fuel metabolism. Lack of insulin leads to mobilization of substrates for gluconeogenesis and ketogenesis from muscle and adipose tissue, accelerated production of glucose and ketones by the liver, and impaired removal of endogenous and exogenous fuels by insulin-responsive tissues. The net results are severe hyperglycemia and hyperketonemia that overwhelm renal removal mechanisms. FFA = free fatty acids.

appropriately take up glucose for storage as glycogen. In addition, glucose uptake by peripheral tissues is impaired by the lack of insulin and by the development of insulin resistance secondary to chronic insulin deprivation and the toxic effects of chronic hyperglycemia. The net result is a gross defect in glucose disposal that can be only partially compensated by renal glycosuria.

In addition to hyperglycemia, fasting free fatty acid levels are also elevated in diabetes, because of accelerated mobilization of fat stores. In type 2 diabetes, elevated free fatty acid levels occur in the presence of normal or even increased insulin levels, suggesting that adipocytes become resistant to insulin's inhibitory effect on lipolysis. This adipocyte resistance ultimately leads to the mobilization and inappropriate deposition of triglyceride into liver and muscle, which in turn is associated with insulin resistance in these organs.

Although free fatty acids are not directly converted to glucose, they do promote hyperglycemia by providing the liver with energy to support gluconeogenesis, as well as by interfering with muscle glucose uptake (predominantly by inhibiting glucose transport). Endogenous insulin secretion in type 2 diabetes provides sufficient portal levels of insulin to suppress the conversion of free fatty acids to ketones in the liver. In type 1 diabetes, however, mobilized free fatty acids are more readily converted to ketone bodies. The combined effects of insulin deficiency and the presence of glucagon suppress fat synthesis in the liver. This suppression of fat synthesis reduces intrahepatic malonyl coenzyme A, which together with carnitine stimulates the activity of hepatic acylcarnitine transferase I and thereby facilitates the transfer of long-chain fatty acids into mitochondria, where they are broken down via β-oxidation and converted to ketone bodies. In addition, hypoinsulinemia, by decreasing ketone turnover, enhances the magnitude of the ketosis for any given level of ketone production. During diabetic ketoacidosis, ketone levels are further increased because of the concurrent release of counter-regulatory hormones. The rise in glucagon accelerates hepatic ketogenesis, whereas elevations of catecholamines, growth hormone, and cortisol act in concert to increase lipolysis and subsequent delivery of free fatty acids to the liver (see Fig. 242–3). The increase in substrate delivery may become so pronounced that it saturates the oxidative pathway, thus leading to hepatic steatosis and severe hypertriglyceridemia.

In addition to disordered glucose disposal, type 1 diabetic patients may exhibit defects in the disposal of ingested proteins and fats as well. In the absence of the normal rise in insulin, meal ingestion may produce hyperaminoacidemia, because of a failure to stimulate the

net uptake of amino acids in muscle, and hypertriglyceridemia, through the reduced activity of lipoprotein lipase. Thus, diabetes should be viewed not only as a disorder of glucose tolerance but also as a disorder of protein and fat tolerance.

Pathogenesis

Type 1 diabetes produces profound β-cell failure with secondary insulin resistance, whereas type 2 diabetes causes less severe insulin deficiency but greater impairment of insulin action. Given their similarities overall, it is not surprising that the two major forms of diabetes share many pathophysiologic features. However, despite the apparent phenotypic similarity, the underlying pathogenetic mechanisms leading to type 1 and type 2 diabetes are strikingly different.

TYPE 1 DIABETES

Type 1 diabetes results from an interplay of genetic, environmental, and autoimmune factors that selectively destroy insulin-producing β cells (see Fig. 242–2).

GENETIC FACTORS. The role of genetic factors in type 1 diabetes is underscored by data in identical twins showing concordance rates of 30 to 40%. It has been assumed that because concordance rates are not 100%, environmental factors must be important for disease expression. Although the presence of an environmental trigger is likely, it should be recognized that even identical twins do not express identical T-cell receptor and immunoglobulin genes; therefore, total concordance would not be expected for autoimmune diseases such as type 1 diabetes.

Many of the genes linked to type 1 diabetes have not been identified, but some are known. HLA genes, located on the short arm of chromosome 6, clearly play a dominant role; in nonaffected siblings, the risk of developing diabetes is 15 to 20% if they are HLA-identical, approximately 5% if they share one HLA gene, and less than 1% if no HLA genes are shared. Specific HLA haplotypes have been linked to type 1 diabetes: 90 to 95% of type 1 patients express DR3 and/or DR4 class II HLA molecules (as compared with 50 to 60% of the general population), whereas 60% express both alleles, a rate more than 10-fold that of the general population. Another class II allele, DQB1*0602, has a negative association with the disease. Specific class II DQ haplotypes (e.g., DQ8 and DQ2) even more strongly correlate with disease susceptibility in caucasian individuals; this susceptibility is associated with polymorphisms of the allele encoding the β-chain of the DQ class II HLA molecule. The presence of aspartic acid at position 57 protects against disease, while substitution of a neutral amino acid at this position is associated with higher disease frequency. Other polymorphisms, such as the substitution of arginine at position 52 of the DQ α-chain, may confer additional risk. Overall, it seems clear that significant genetic heterogeneity exists, and that no single class II HLA gene accounts for all HLA-associated susceptibility to disease. Association of the disease with specific class II HLA genes implies the involvement of CD4+ T cells in the autoimmune process, because these molecules are critical for both the presentation of antigenic peptides to CD4+ T cells and the selection of the CD4+ T-cell repertoire in the thymus.

Other genes likely to contribute genetic susceptibility to type 1 diabetes include *IDDM 2* (chromosome 11p), a noncoding promoter region of the insulin gene that may influence insulin gene expression in the thymus (and may therefore affect thymic selection of insulin-reactive T cells), and *CTLA-4* (chromosome 2q), which plays a role in T-cell action and regulation. Many other genes have also been implicated, underscoring the polygenic nature of this disease.

ENVIRONMENTAL FACTORS. Although environmental factors such as diet and toxins have been proposed as triggers of diabetes, most of the scientific attention has focused on putative viruses. Epidemics of mumps, congenital rubella, and coxsackievirus have been associated with an increased frequency of type 1 diabetes. In one instance, coxsackievirus B4 was isolated from the pancreas of a child who died of diabetic ketoacidosis, and inoculation of the virus into mice caused diabetes, fulfilling Koch's postulates. However, it is likely that acute, lytic viral infections are responsible for only an occasional case of diabetes. Instead, if viruses are involved, it is far more likely that they trigger an autoimmune response. If a virus contains an epitope resembling a β-cell protein, viral infection could theoretically abrogate self-tolerance and trigger autoimmunity.

AUTOIMMUNE FACTORS. About 80% of patients with new-onset type 1 diabetes have islet cell antibodies. Antibodies to a variety of β-cell constituents have been identified, including insulin, isoforms of glutamic acid decarboxylase (GAD 65 and GAD 67), and the secretory granule protein ICA 512 or IA-2, which contains a tyrosine phosphatase-like domain. The idea that type 1 diabetes is a chronic autoimmune disease with acute manifestations is supported by the fact that islet antigen-directed antibodies are present in approximately 3% of asymptomatic first-degree relatives of patients; such antibody-positive individuals are at high risk for the development of type 1 diabetes, although clinical onset may be delayed by many years. The likelihood of type 1 diabetes is greater than 50% if autoantibodies are present to more than one β-cell antigen (i.e., insulin, GAD 65, ICA 512), whereas diabetes rarely develops in antibody-negative relatives. If antibodies appear at a young age, the risk for clinical diabetes is particularly high.

The listed antibodies appear to be markers for, rather than the cause of, β-cell injury. β-Cell destruction (by apoptotic and cytotoxic mechanisms) is mediated by a variety of cytokines, or by direct T lymphocyte activity. Supporting this notion, type 1 diabetes has been transferred through bone marrow cells from a diabetic patient to a nondiabetic recipient. Additionally, autopsies performed on patients dying soon after disease onset have shown islet-restricted monocytic cellular infiltrates (termed insulitis) that are composed of CD8+ and CD4+ T cells, macrophages, and B cells. Usually, as the disease progresses, the islets become completely devoid of β cells and inflammatory infiltrates; α, δ, and pancreatic polypeptide cells are left intact, thus illustrating the exquisite specificity of the autoimmune attack. At the time of clinical diagnosis, about 5 to 10% of the original β-cell mass typically remains (see Fig. 242–2).

A critical role for T cells is supported by studies involving pancreatic transplantation in identical twins. Monozygotic twins with diabetes who received kidney and pancreas grafts from their nondiabetic, genetically identical sibling required little or no immunosuppression for graft acceptance. Nevertheless, the islets were soon selectively invaded with mononuclear cells, predominantly CD8+ T cells, with the subsequent recurrence of diabetes. Thus, decades after the original onset of disease, the immune system retained the ability to selectively destroy β cells. Evidence implicating T cells also derives from clinical trials using immunosuppressive drugs. Drugs such as cyclosporine slow or prevent the progression of recent-onset diabetes, but immunosuppression must be continuous to maintain the effect. Further supporting data for a primary role for T cells derives from NOD mice, in which insulitis and islet autoantibodies develop at about 4 weeks of age, and diabetes ultimately develops after 12 to 24 weeks; in these mice, a variety of treatments designed to deplete T cells can prevent diabetes. Most importantly, adoptive transfer of T cells isolated from diabetic mice donors into immune-incompetent NOD mice rapidly produces diabetes. Both CD4+ and CD8+ T cells are generally required for transfer of disease, which suggests that both are necessary for disease expression. These diabetogenic T cells target specific β-cell antigens, including insulin and GAD. A likely role for GAD and/or insulin is also suggested by data showing that if NOD mice are made tolerant to GAD or to insulin (or to peptides derived from these molecules) early in life, insulitis and diabetes fail to develop. Finally, the chronic, smoldering nature of type 1 diabetes suggests the presence of regulatory or protective influences. In keeping with this observation, T cells that protect the islet cell from immune attack have been isolated from the islets of NOD mice. Such findings suggest that the rate of appearance and clinical expression of disease may be modulated by the balance between diabetogenic and protective populations of T cells. "Tipping the scales" in favor of protective T-cell proliferation is the goal of protective immunization.

TYPE 2 DIABETES

Hyperglycemia in type 2 diabetes likely results from complex genetic interactions, the expression of which is modified by environmental factors such as body weight and exercise. With type 2 diabetes, identical twin concordance rates approach 100%, although disease onset and course can vary greatly based on environmental factors. Hyperglycemia itself is known to impair insulin secretion and action; elevated free fatty acid levels also play a pathogenic role. By the time that hyperglycemia is detected, nearly all type 2 patients exhibit both defective insulin secretion and insulin resistance; this makes it

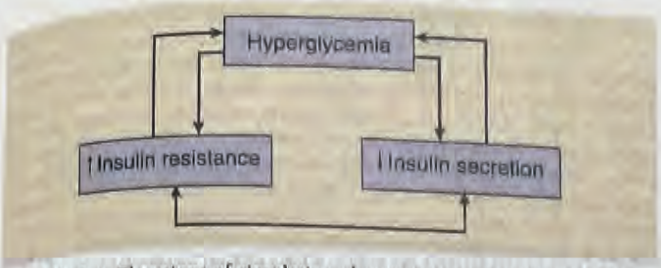

FIGURE 242–4 • Elevations of circulating glucose initiate a vicious cycle in which hyperglycemia begets more severe hyperglycemia.

difficult to determine which of the two factors is primarily responsible for the vicious cycle leading to disease (Fig. 242–4).

GENETIC FACTORS. Although monogenic forms of diabetes have been identified (e.g., MODY types 1 through 6), the vast majority of cases are polygenic in nature. Type 2 diabetes shows clear familial aggregation but does not segregate in classic mendelian fashion; this implies that the disease results either from a combination of genetic defects or from the simultaneous presence of multiple susceptibility genes in the presence of predisposing environmental factors. Candidate gene mutations for polygenic forms of type 2 diabetes include mutations of the coding region of the insulin gene, peroxisome proliferator-activated receptor gamma (PPAR-γ), intestinal fatty acid binding protein 2 (FABP 2), calpain 10, and the β-3-adrenergic receptor. These and other mutations have been associated with isolated patient clusters of type 2 diabetes.

INSULIN SECRETION. Fasting insulin levels in type 2 diabetes are generally normal or elevated, yet they are *relatively* low given the degree of coexisting hyperglycemia. As the disease progresses and hyperglycemia becomes more severe, basal insulin levels eventually fail to keep up and may even decline. The insulin secretory defect usually correlates with the severity of fasting hyperglycemia and is more evident following carbohydrate ingestion. In its mildest form, the β-cell defect is subtle, involving the loss of the first-phase insulin response and the normal oscillatory pattern of insulin secretion. Although the overall insulin response may be fairly intact, this "normal" response is actually inadequate to maintain glucose tolerance when viewed in the context of simultaneous insulin resistance. During this early stage, the β-cell defect is usually specific for glucose; other secretagogues (e.g., amino acids) maintain their potency, and insulin deficiency is thus less pronounced during the ingestion of mixed meals. Patients with more severe fasting hyperglycemia lose this capacity to respond to the other insulin secretagogues; thus, their secretory defect worsens as their disease progresses. Unfortunately, the underlying cause of the secretory defect remains uncertain and is likely multifactorial.

Studies in rodents suggest that the loss of glucose-stimulated insulin secretion is followed by a decreased expression of GLUT 2, the primary glucose transport protein of the pancreatic β-cell. Such a loss of GLUT 2 during the clinical transition to diabetes would likely accelerate the decline of glucose-stimulated insulin secretion. Pathologic studies of islets from patients with long-standing type 2 diabetes have demonstrated amyloid-like deposits composed of islet amyloid polypeptide, or *amylin*, a peptide synthesized in the β-cell and cosecreted with insulin. Chronic hypersecretion of amylin may lead to precipitation of the peptide, which over time might also contribute to impaired β-cell function. Recent experiments in gene knockout mice suggest a potential role for impaired insulin receptor signaling in the development of impaired β-cell function. A link between insulin resistance and secretion is also suggested by data showing that accumulation of fat within the β-cell (as a result of hyperglycemia, insulin resistance, and increased fatty acid turnover) may further reduce insulin secretion.

INSULIN RESISTANCE. With few exceptions (e.g., a subgroup of African American patients), type 2 diabetes is characterized by impaired insulin action. The insulin dose-response curve for augmenting glucose uptake in peripheral tissues is shifted to the right (representing decreased insulin sensitivity), and maximal response is reduced, particularly in the setting of severe hyperglycemia. Other insulin-dependent processes, such as inhibition of hepatic glucose production and lipolysis, also show reduced sensitivity to insulin. The mechanisms responsible for insulin resistance remain poorly understood.

Early studies of insulin resistance focused on defects of the insulin receptor. Mutation of the insulin receptor gene can produce leprechaunism, characterized by severe growth retardation, extreme insulin resistance, and early infant death. Other syndromes related to mutated insulin receptors include the Rabson-Mendenhall syndrome, also associated with tooth and nail abnormalities and pineal gland hyperplasia, and "type A insulin resistance," most often affecting young females with acanthosis nigricans, polycystic ovaries, and hirsutism. Another example of extreme insulin resistance involves the presence of anti-insulin receptor antibodies, which is associated clinically with acanthosis nigricans and other autoimmune phenomena.

Although insulin receptors are rarely abnormal in type 2 patients, defects in more distal "post-receptor" pathways play a far greater role in insulin resistance. One important aspect of resistance is a reduced capacity for translocation of GLUT 4 to the cell surface in muscle cells. A separate defect in glycogen synthesis is also likely to be present. Whether the defects uncovered are primary or secondary to the disturbance in glucose metabolism is uncertain; possibly, a variety of genetic abnormalities in cellular transduction of the insulin signal may individually or in concert produce an identical clinical phenotype. It is uncertain whether mechanisms of insulin resistance in nonobese patients are identical to those of their obese counterparts; however, the coexistence of obesity clearly accentuates the severity of the resistant state. In particular, upper body or abdominal (as compared with lower body or peripheral) obesity is associated with insulin resistance and diabetes. Intra-abdominal visceral fat deposits, detected by computed tomography or magnetic resonance imaging, have a higher lipolysis rate and are more resistant to insulin than peripheral fat. The resulting increase in circulating free fatty acid levels promotes fat deposits in the liver and muscle, worsening insulin resistance. Intracellular free fatty acid metabolites appear to promote insulin resistance through complex mechanisms, involving serine (rather than tyrosine) phosphorylation of insulin signaling molecules. Cortisol hypersecretion and/or hereditary factors may also influence the distribution of body fat, the latter contributing an additional genetic influence on the expression of disease.

ADIPOCYTE-DERIVED HORMONES AND CYTOKINES. Adipocytes, once thought of as inert fat storage cells, are now known to produce a number of metabolically active hormones that may affect insulin sensitivity. *Leptin*, for example, acts on the hypothalamus to promote satiety and energy expenditure and may accelerate glucose metabolism. *Adiponectin* (Acrp30), another fat-derived hormone, circulates at levels that correlate inversely with both adiposity and degree of insulin resistance. The administration of adiponectin to obese mice causes a transient, dose-dependent, insulin-independent decrease in circulating glucose levels; adiponectin also improves insulin sensitivity by decreasing triglycerides in the liver and muscle, likely by increasing the expression of molecules involved in fatty acid combustion and energy dissipation. Finally, adipose tissue is an abundant source of the cytokine tumor necrosis factor-α, which is known to inhibit muscle glucose metabolism by inducing serine phosphorylation of insulin signalling molecules. The precise impact that these and other adipocyte-derived factors exert on insulin resistance has yet to be established; these proteins may well play an important role in the pathogenesis of diabetes.

GLUCOTOXICITY AND LIPOTOXICITY. Hyperglycemia per se impairs the β-cell response to glucose and promotes insulin resistance. Reversal of glucotoxicity can disrupt the vicious cycle that perpetuates hyperglycemia (see Fig. 242–4). Circulating lipids can also adversely affect glucose metabolism; increased free fatty acid levels accelerate hepatic gluconeogenesis, inhibit muscle glucose metabolism, and may impair pancreatic β-cell function. As is the case with glucotoxicity, the reversal of lipotoxicity can rapidly improve metabolic control and facilitate favorable therapeutic outcomes.

WHAT IS THE PRIMARY DEFECT? It remains uncertain whether insulin resistance or defective insulin secretion is the primary defect in type 2 diabetes. This issue is difficult to resolve once diabetes has developed; therefore, research attention has focused primarily on high-risk, nondiabetic subjects. Studies in high-risk populations (e.g., Pima Indians, Mexican Americans) have suggested that insulin resistance is the initial defect; similar findings have been reported in first-degree relatives of type 2 diabetic patients and in healthy prediabetic offspring of two diabetic parents. Interestingly, hyperinsulinemia has been detected in prediabetic subjects as early as one to two decades before clinical onset, suggesting that the development of diabetes can be exceedingly slow. Although these studies support the view that

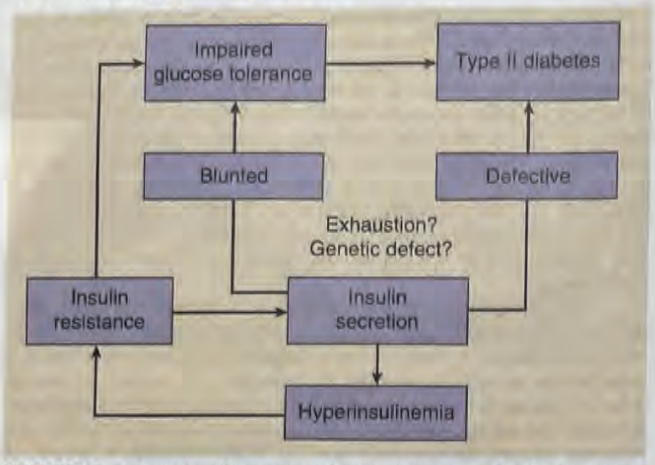

FIGURE 242–5 • A proposed sequence of events leading to the development of type 2 diabetes: insulin resistance resulting from genetic influences, central obesity, inactivity, or a combination of these factors leads over time to a progressive loss of the β-cell's capacity to compensate for this defect.

insulin resistance generally antedates insulin deficiency, the presence of insulin resistance alone is generally insufficient to generate disease; this implies that for diabetes to occur, impaired insulin secretion is also required (Fig. 242–5). It is possible that the appearance of a secretory defect is a secondary phenomenon, possibly resulting from "β-cell exhaustion," excess fatty acid delivery, and/or amylin accumulation. Alternatively, diminished insulin secretion may result from an independent defect that becomes evident only upon chronic β-cell stimulation, such as a subtle genetic defect in insulin signaling.

The sequence of events described—underlying insulin resistance followed by a secretory defect—is common but clearly does not describe all type 2 diabetic patients. For example, a subgroup of African American patients exhibits little or no insulin resistance. Additionally, diminished glucose-stimulated insulin secretion is seen in women with gestational diabetes in whom type 2 diabetes later develops. Finally, the demonstration of functional β-cell–associated gene mutations in patients with MODY indicates that primary β-cell defects are capable of producing a similar phenotype. Taken together, these lines of evidence strongly suggest that type 2 diabetes cannot be explained by insulin resistance alone or by any single pathogenic mechanism.

Relationship Between Diabetes Control and Its Complications

Whether the vascular and neuropathic complications of diabetes mellitus can be prevented or delayed by improved glycemic control was debated for more than a half century. To answer the question, the National Institutes of Health initiated the Diabetes Control and Complications Trial (DCCT), a 9-year multicenter study involving 1441 type 1 patients aged 13 to 39 years who were randomly assigned to either intensive insulin therapy or conventional care. Intensive therapy consisted of three or more insulin injections per day (or an insulin pump), self-monitoring of blood glucose at least four times per day, and frequent contact with a diabetes health care team. Conventional care consisted of one or more (commonly two) injections of insulin per day, less frequent glucose monitoring, standard education, and less frequent health care visits. The target goals of therapy were different as well. The intensive therapy group sought pre-meal blood sugar levels of 70–120 mg/dL, postprandial blood levels of less than 180 mg/dL, and glycohemoglobin values as close to normal as possible. In the conventional care group, the primary goal was simply to maintain clinical well-being. Patients were divided into two groups: (1) a primary prevention group, with diabetes for 1 to 5 years and no detectable complications, and (2) a secondary intervention group, with diabetes for 1 to 15 years and mild nonproliferative retinopathy. Remarkably, nearly 99% of enrolled patients completed the trial.

The DCCT achieved a clear separation of glucose levels between the groups over the entire study period. Glycohemoglobin (Hb A_{1c}) and mean glucose levels in the intensive therapy group were 1.5 to 2.0% and 60 to 80 mg/dL lower than in those receiving conventional care. Although considerable variability was noted among individual patients, most of the intensive care group failed to achieve normal glucose levels (glycohemoglobin averaged 1.1% above normal, or a glucose level of about 155 mg/dL). Nevertheless, intensive therapy reduced the development of retinopathy by 76% in the primary prevention group, and the progression of retinopathy by 54% in the secondary intervention group (Fig. 242–6) ■; the latter effect became apparent after only 4 years. In addition, intensive therapy reduced the risk of microalbuminuria by 39%, frank proteinuria by 54%, and clinical neuropathy by 60%. The incidence of major cardiovascular events also tended to be lower, but the number of events was insufficient for statistical proof; at the very least, intensive therapy did not pose a *risk* for macrovascular complications. An exponential relationship over time between the average blood glucose level (as reflected by Hb A_{1c}) and the progression of retinopathy in the intensive care group suggests that there may be no threshold level at which complications occur. These findings imply that *any degree of improvement in glycemic control has benefit*, and that normalization of glucose levels is not required to slow the progression of diabetic complications.

The benefits achieved by intensive control in the DCCT were not without risk. Weight gain was more common, and most importantly, the frequency of severe hypoglycemia (including multiple episodes in some patients) was three-fold higher in the intensive care group. In many cases, such episodes occurred without classic warning symptoms, often while the patient was asleep. Thus, in some patients, the risks of intensive therapy may outweigh the benefits; possibly included are patients with recurrent severe hypoglycemia, patients with advanced complications, young children, and patients who are unable or unwilling to participate in their management (e.g., self-monitoring of blood glucose). Such individuals are likely to benefit from less aggressive therapy designed to moderately lower glucose levels without the risk of hypoglycemia. It is noteworthy that despite

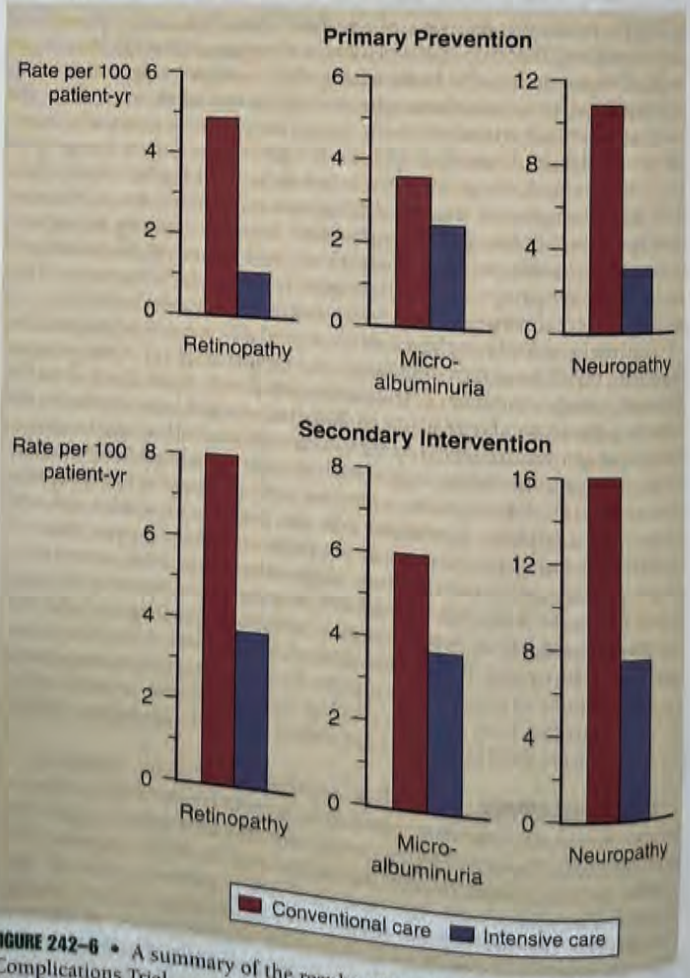

FIGURE 242–6 • A summary of the results of the Diabetes Control and Complications Trial.

the higher rate of hypoglycemia, intensive therapy in the DCCT had no detectable long-term effects on cognitive function.

Although the DCCT did not involve type 2 diabetic patients, a small study using a similar experimental design in lean Japanese patients with type 2 diabetes showed similar results. More conclusive evidence that improved control of blood glucose is beneficial for type 2 diabetic patients derives from the United Kingdom Prospective Diabetes Study (UKPDS). The UKPDS recruited 5102 patients with newly diagnosed type 2 diabetes between 1977 and 1991. After 3 months of diet therapy, the 3867 patients with fasting glucose levels between 6.1 and 15.0 mmol/L (110 and 270 mg/dL) were randomized to a more intensive regimen consisting of sulfonylurea, metformin (for obese patients only) or insulin, or a conventional treatment regimen focused primarily on symptom reduction. Subjects were monitored for an average of 10 years. Although glycemic control gradually deteriorated in both groups, the intensified treatment group had lower mean Hb A_{1c} than their conventionally treated counterparts (7.0% versus 7.9%). This modest improvement significantly reduced microvascular complications by 25% and reduced all diabetes-related events by 12%. The intensified treatment group also had a 16% reduction in a combined end point—nonfatal or fatal myocardial infarction or sudden death—that did not quite reach statistical significance ($P = .052$). A continuous relationship was again noted between glycemic control and diabetic complications; also similar to the DCCT, no glycemic threshold for microvascular complications was observed. Importantly, serious adverse events were rare for all of the treatment arms in the UKPDS, and only a single death from hypoglycemia occurred in more than 27,000 patient years of intensive therapy.

What conclusions can be drawn from the DCCT and the UKPDS? The primary message is that "glucose matters." In both type 1 and type 2 diabetic patients who are willing and able to actively participate in their management, the goal should be to achieve the best possible level of glycemic control as rapidly as possible without undue risk. The DCCT and UKPDS also demonstrate that most patients benefit from lower glucose levels, even if normalization is not achieved; for most type 2 patients, effective glucose reductions can be achieved by diet, oral agents, or less complicated insulin regimens than are required in type 1 patients. The greatest challenge for the clinician is how to effectively apply the DCCT and UKPDS results in practice, a formidable task. Both study groups were highly motivated and compliant. Furthermore, management was supervised by an experienced health care team that was able to devote more time to patients than is usually feasible. An important lesson from these studies was that successful treatment of diabetes was largely accomplished through the efforts of the patients themselves, as well as by nurse educators, dietitians, and diabetes counselors. It makes sense, then, to encourage the use of physician-directed health care *teams* to translate the findings of the DCCT and UKPDS into clinical practice.

Rx Treatment

Treatment of diabetes mellitus involves changes in lifestyle and may require pharmacologic intervention with insulin or with oral glucose-lowering drugs. In type 1 diabetes, the primary focus is to replace lost insulin secretion; lifestyle changes are required to facilitate insulin therapy and to optimize health. For patients with type 2 diabetes, changes in lifestyle are the cornerstone of treatment (especially in the early stages of disease), and pharmacologic intervention is a secondary treatment strategy. Although therapeutic strategies differ for the two common forms of diabetes, the treatment goals are essentially identical. In the short term, the goals of diabetes treatment are to optimize metabolic control and improve the patient's sense of clinical well-being. Long-term therapeutic goals focus on the prevention of complications, including cardiovascular disease, nephropathy, retinopathy, and neurologic disease.

TYPE 1 DIABETES

INSULIN PREPARATIONS AND PHARMACOKINETICS. A variety of highly purified insulin preparations are commercially available that differ mainly in their pharmacokinetics (Table 242–5). Premixed insulin preparations are also available and may offer added convenience for selected patients. Nearly all insulin preparations contain 100 U/mL (U-100), although a more concentrated 500 U/mL preparation of regular insulin (U-500) for severely resistant patients can be obtained. Human insulin is now the only form of insulin sold in North America and other industrialized countries, largely because of immunologic concerns. Because human insulin generates lower titers of insulin antibodies than porcine or bovine insulin, it acts more rapidly after injection and has a shorter duration of action, allowing better synchrony between insulin peaks (after premeal injection of rapid-acting insulin) and the absorption of meals. It is noteworthy that the same insulin preparation can produce variable responses in a single patient, since the peak and duration of most insulin preparations are influenced by the site of administration, skin temperature, the depth of injection, and the magnitude of the insulin dose.

Table 242–5 • INSULIN PREPARATIONS: EFFECT ONSET, PEAK, AND DURATION AFTER SUBCUTANEOUS ADMINISTRATION

CLASS	PREPARATION EFFECT	ONSET OF EFFECT	PEAK (HRS)	DURATION OF ACTION (HRS)
Rapid-acting	Lispro or Aspart	10–15 min	1–2	3–4
Short-acting	Regular (R)	30 min	2–4	5–8
Intermediate-acting	NPH (N) or Lente	2–4 hours	5–10	16–20
Long-acting	Ultralente (U)	4–6 hours	6–16	~24
	Glargine	2–4 hours	no peak	>30

Rapid- and Short-Acting Insulin Preparations. After subcutaneous injection, regular (R) insulin begins to act in about 30 minutes and should therefore be administered 25 to 30 minutes before a meal. Because it acts quickly and has a relatively short duration of action (5–8 hours), it is effective for blunting postprandial glucose excursions and for facilitating rapid dose adjustments based on measured blood glucose values. The properties of regular insulin are especially helpful in managing glucose elevations that occur during illness, or after the consumption of large meals. Given intravenously, regular insulin is also effective in the perioperative period and in the management of severely ill patients and acute hyperglycemic complications.

In regular insulin preparations, insulin molecules exist predominantly in hexameric form. Before being absorbed, insulin hexamers must first be diluted in subcutaneous interstitial fluid, then dissociate into single molecules; this property accounts for the slightly delayed absorption of regular insulin from subcutaneous injection sites. Recently, advances in recombinant DNA technology have led to the development of insulin analogues intended to bypass this property, allowing for more rapid absorption. In 1996, lispro insulin was introduced. This insulin analogue, in which the amino acids in positions B28 (lysine) and B29 (proline) have been reversed, has a reduced capacity for hexameric self-association and is therefore more rapidly absorbed. Its effects begin within 10 to 15 minutes of administration, and generally wane within 3 to 4 hours. Because of its rapid onset, lispro can be given just before eating (as opposed to 30 minutes prior), a feature that greatly simplifies the planning and consumption of meals; also, because its effects wane more rapidly, there is a reduced risk of "late" hypoglycemia if the next meal is delayed. Using lispro insulin, postprandial glucose and hemoglobin A_{1c} reductions are equal to or better than those achieved with regular insulin, and there is a reduced incidence of delayed hypoglycemia. For these reasons, and because of greater convenience and flexibility, lispro is being used with increasing frequency in intensive treatment regimens.

Insulin aspart, the second rapid-acting insulin analogue approved by the Food and Drug Administration (FDA), was released in 2001. In insulin aspart, a neutral proline residue at position B28 is replaced by negatively charged aspartic acid, resulting in a reduced capacity for self-association and faster absorption. The pharmacokinetic properties of insulin aspart are similar to those of insulin lispro; insulin aspart may have a slightly longer duration of effect.

Intermediate- and Long-Acting Insulin Preparations. The longer-acting insulin preparations have been modified to delay their absorption from injection sites, resulting in a longer duration of insulin activity. The addition of protamine and zinc yields intermediate-acting Neutral Protamine Hagedorn (NPH) insulin, whereas enlarging the size of the zinc-insulin crystal yields Lente (intermediate-acting) and Ultralente (long-acting) insulins. NPH and Lente, the

intermediate-acting insulins, have a similar time course of action, when given twice per day, they offer a compromise between some degree of meal coverage (coinciding with peak activity) and the provision of basal insulin levels. Ultralente insulin, because of its longer duration and somewhat less evident peaks, offers possible advantages for basal insulin replacement and can be given once daily in some patients. However, the pharmacokinetics of Ultralente are less predictable in clinical practice (even within a single patient), and its effects commonly require twice-daily dosing, limiting its utility.

Insulin glargine, approved by the FDA in 2001, differs from human insulin both at position A21, where asparagine is replaced by glycine, and at the C-terminus of the B-chain, where two arginine residues have been added. Insulin glargine is soluble at acidic pH and less so in physiologic conditions; injected at a pH of 4, it is neutralized in subcutaneous tissue and forms microprecipitates, delaying its absorption and prolonging its duration of activity. The primary advantages of glargine insulin are greater than 24-hour activity (allowing once-daily dosing) and the lack of peak concentrations; both characteristics are desirable for the provision of consistent basal insulin levels. Disadvantages include higher cost, a higher incidence of mild injection site discomfort, and the inability to mix glargine with other insulins. Clinical trials in type 1 diabetic patients suggest that insulin glargine produces similar or slightly larger reductions in hemoglobin A_1, as compared with NPH; comparative trials have also shown a reduced incidence in nocturnal hypoglycemia when insulin glargine is used. In type 2 diabetic patients, the clinical differences between glargine and NPH are less significant; in comparative trials, hemoglobin A_1, reductions are generally equivalent, and there are smaller differences in the incidence of hypoglycemia. Other long-acting insulins, intended for use in basal insulin therapy, are currently in development.

INSULIN REGIMENS. While a simple concept, the clinical use of insulin to treat diabetes mellitus can be extraordinarily complex. There are many important inter-patient (and intra-patient) variables, so a predictable algorithm cannot be uniformly applied to all patients, nor to a single patient at all times. In general, subcutaneous insulin regimens for type 1 diabetes may be classified as "conservative" or "intensive." Modes of continuous subcutaneous insulin infusion (i.e., insulin pumps) have also gained popularity in recent years.

Conservative Insulin Therapy. Through the early stages of type 1 diabetes, some degree of β-cell function is usually preserved, allowing many patients to achieve glycemic control with less intensive effort. Because intermediate-acting insulins are not generally sustained over a 24-hour period, and because insulin requirements tend to increase early in the morning, these patients should start with two daily injections, consisting of a mixture of intermediate-acting and rapid-acting human insulins administered before breakfast and before dinner. Although Lente insulin has a theoretic advantage over NPH in that it does not contain a foreign protein (protamine), this difference seems to have negligible clinical significance. In fact, NPH may be preferable to Lente when insulins are mixed, because the excess zinc in Lente preparations can cause regular insulin to precipitate out of solution, delaying its absorption.

There are many acceptable approaches to the initiation of conventional insulin therapy (see the section on the treatment of type 2 diabetes). Regardless of the initiation method used, insulin dose adjustments will inevitably be required. Initially, doses of the intermediate-acting insulin should be adjusted to optimize pre-dinner and fasting (morning) glucose levels. Once these goals are accomplished, rapid-acting insulin doses should then be adjusted to optimize postprandial, pre-lunch, and bedtime glucose values. Patients should generally inject in the same anatomic region at the same time each day (i.e., in the abdomen in the morning, in the thigh at night) to ensure consistent insulin delivery; an effort should also be made to avoid exact duplication of injection sites within a 1-week period. Some patients may experience a brief "honeymoon" period, during which β-cell function partially recovers and insulin needs are temporarily reduced. Such an improvement should not be used as a signal to reduce efforts aimed at glycemic control, since continuation of optimal insulin therapy will help to preserve residual β-cell function.

Multiple Subcutaneous Injections. Several years after the onset of type 1 diabetes, residual insulin secretion typically ceases. When this occurs, twice-daily insulin injections are no longer acceptable, even if they continue to successfully control diabetic symptoms. For optimal glycemic control, insulin delivery should more closely simulate the "normal" pattern of insulin secretion; namely, continuous or "basal" insulin levels are required throughout the day, while brief increases in insulin levels ("boluses") should coincide with the ingestion of meals. The primary problem with twice-daily insulin regimens is that the glucose-lowering effect of the pre-dinner intermediate-acting insulin is greatest at the time when insulin requirements are at their lowest (i.e., around 3:00 AM). Additionally, when requirements are increasing in the pre-dawn hours, insulin levels are declining. The net results of this poorly matched insulin supply and demand are the production of nocturnal hypoglycemia and/or fasting (morning) hyperglycemia.

Successful management of diabetes begins with fasting glucose control. Failure to control morning sugars often results in the stubborn perpetuation of hyperglycemia throughout the day. Once hepatic gluconeogenesis has been activated in the morning, it is not readily suppressed by insulin injections. The key factors responsible for fasting hyperglycemia are inadequate overnight delivery of insulin and sleep-associated growth hormone release. The "dawn phenomenon" is most pronounced in patients with type 1 diabetes because of their inability to compensate by raising endogenous insulin secretion. The magnitude of the dawn phenomenon can be attenuated by designing insulin regimens to ensure that the effects of exogenous insulin do not peak in the middle of the night and dissipate by morning. Several approaches to insulin therapy can deal with this problem; some of the more common regimens are displayed in Figure 242–7. One common approach is to use three injections: a mixture of intermediate- and rapid- or short-acting insulin before breakfast, rapid- or short-acting insulin before dinner, and intermediate-acting insulin at bedtime. The primary disadvantage of this approach is that meal sizes and schedules must be fixed rather rigidly. Alternative multidose regimens incorporate short- or rapid-acting insulin injections before each meal, with one or two daily doses of intermediate- or long-acting insulin (e.g., glargine). Pen-style insulin injectors are also available; these may help to make multidose regimens more convenient and tolerable for patients.

Continuous Subcutaneous Insulin Infusion (CSII). In CSII, rapid-acting insulin is administered around the clock by a battery-powered, externally worn, computer-controlled infusion pump (see Fig. 242–7). The

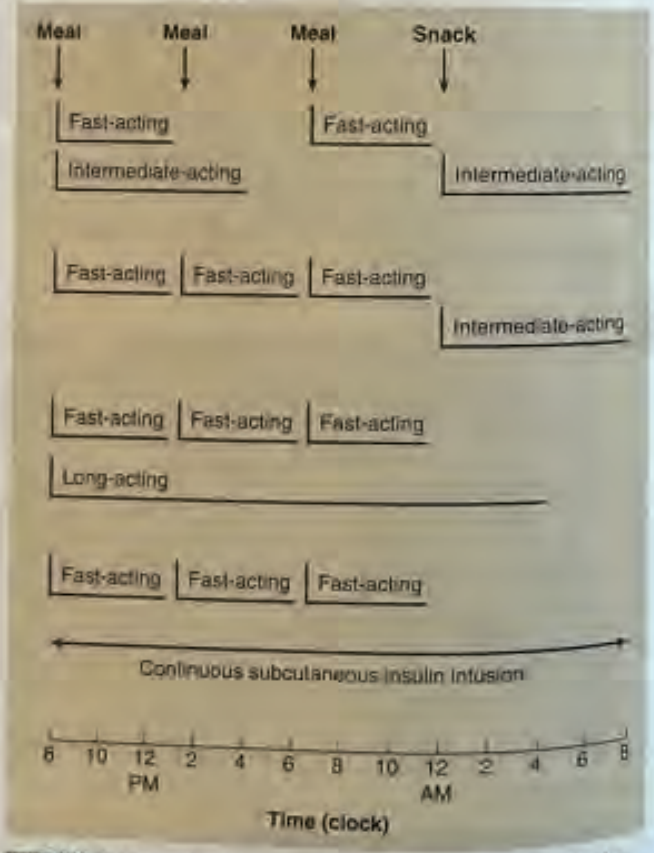

FIGURE 242–7 ▸ Several intensive insulin regimens commonly used in the treatment of diabetes. Each is designed to provide a continuous supply of insulin around the clock and to make extra insulin available at the time of meals, thereby simulating more closely the normal physiologic pattern of insulin secretion.

pump delivers a continuous basal rate and can be programmed to vary the flow rate automatically for set time periods, such as reducing the flow rate after bedtime and increasing flow to compensate for increased insulin requirements in the pre-dawn hours. Boluses, determined by self-monitoring of blood glucose and expected meals, are given by manual pump activation. Most insulin pumps contain an insulin reservoir attached to a subcutaneous catheter (the catheter is inserted using an introducing needle, which is then removed). Catheters are generally best placed in the abdomen, to standardize absorption and maximize visibility. Overall, the CSII method provides diabetic patients with the highest degrees of lifestyle flexibility and glucose control.

The CSII approach has several limitations. One obvious disadvantage of pump therapy is the wearing of the pump itself; the device may be undesirable for patients during intense exercise, contact sports, submersion in water, or personal intimacy. Furthermore, because CSII uses rapid- or short-acting insulin, any interruption in flow (most commonly because of insulin precipitation within the catheter) can lead to rapid deterioration of metabolic control. Local infections at the catheter site occasionally occur, necessitating a site change every 2 to 3 days. Furthermore, maintenance of the pump and appropriate insulin infusion rates requires significant patient effort and sophistication.

The intensive treatment regimens described above are not for everyone. In appropriate patients, however, intensive insulin therapy should be strongly encouraged to reduce the risk of late diabetic complications. It should also be noted that pregnancy is an absolute indication for intensive therapy, and that reduction of the excess neonatal morbidity and mortality associated with diabetic pregnancies requires tight glycemic control. Ideally, intensive insulin therapy should be instituted in type 1 patients before conception, to minimize the risk of fetal anomalies. After conception, blood glucose targets are more stringently applied than at other times, with the specific aim of maintaining glucose levels in the normal range.

LIFESTYLE CHANGES. Diet and exercise contribute importantly to the care of patients with type 1 diabetes. Patients should be educated about balancing caloric intake (diet) with energy expenditure (exercise) and should understand the basic concepts of insulin therapy as it relates to stress and physical activity. If properly managed and sufficiently motivated, diabetic patients should be able to consume the foods they enjoy and should be able to fully participate in exercise and sports.

Diet. The introduction of intensive insulin regimens has increased meal flexibility by allowing more latitude in varying the size, content, and timing of meals. New approaches offer the opportunity for a more normal lifestyle, thus minimizing compliance problems and optimizing patient acceptance and satisfaction. Meals should be nutritionally sound and should provide sufficient calories to meet the energy needs of growing children, active young adults, and pregnant women; the 1800-kcal diet classically prescribed for type 2 patients is grossly insufficient in these and other individuals. Furthermore, diabetic diets should be specifically aimed at minimizing long-term cardiovascular risk by minimizing the ingestion of sodium, cholesterol, and saturated fats (Table 242–6).

Because type 1 patients depend on exogenous insulin, proper management is facilitated by a meal plan designed to match the time course of the selected insulin regimen. Patients should learn to compensate for meal-plan departures by adjusting their insulin doses and for periods of altered activity by adjusting their consumption of food. Effort should be made to avoid long delays between meals, and small snacks may be needed at times of peak insulin action to avoid hypoglycemia. Most patients, regardless of their regimen, should incorporate a bedtime snack to reduce the risk of nocturnal hypoglycemia. Finally, the potential for insulin-induced weight gain requires special emphasis on portion control; to control hypoglycemia, patients should master the use of appropriate carbohydrate intake and avoid overcompensation.

Exercise. Regular exercise is important to promote overall health and to reduce cardiovascular complications. Surprisingly, there is little evidence to suggest that exercise itself substantially improves glycemic control in type 1 diabetes, although it is known to reduce overall insulin requirements by enhancing insulin sensitivity. Through accelerated insulin absorption (due to increased local blood flow at the injection site) and increased muscle glucose consumption, exercise can rapidly reduce blood glucose levels, particularly when it coincides with the peak action of an insulin injection. In nondiabetic individuals, blood glucose levels remain stable during exercise; as decreased endogenous insulin secretion promotes increased hepatic glucose production to match the increased rate of glucose consumption. In diabetic patients receiving exogenous insulin, however, this "finely tuned" homeostatic mechanism is greatly disturbed. The continued presence of exogenous insulin during exercise further accelerates glucose uptake and (more importantly) blocks the compensatory increase in glucose production; as a result, circulating glucose levels can fall precipitously during exercise. Because the magnitude of this fall is not easily titrated, hypoglycemia may occur if the patient is unable to appropriately adjust diet and insulin before, during, and after physical activity (Table 242–6).

Table 242–6 • LIFESTYLE MODIFICATIONS FOR PATIENTS WITH DIABETES

I. Dietary prescription
   1. Weight reduction, gain, or maintenance, to achieve and maintain ideal body weight
   2. Restriction of saturated fat to <10% of total calories, to be replaced in the diet by carbohydrates and monounsaturated fats. If LDL reduction is also desired, saturated fats should be further restricted to <7% of daily caloric intake
   3. Decreased cholesterol intake to <300 mg per day. If LDL reduction is also desired, cholesterol intake should be further restricted to <200 mg per day
   4. Sodium restriction (<2.4 g per day) in patients with hypertension. In those with overt nephropathy, sodium intake should be further restricted to <2.0 g per day
   5. Protein restriction to <20% of total calories; with nephropathy, protein intake should be further restricted to <0.8 mg/kg/day, or to ~10% of daily caloric intake

II. Exercise prescription*
   1. A combination of aerobic exercise and resistance training is preferred. Avoid heavy lifting, straining, and Valsalva maneuvers, which can raise blood pressure and may aggravate proliferative diabetic retinopathy.
   2. Intensity: Increase heart rate "moderately" to at least 55% of "maximal" heart rate (220 minus age in years), with adjustments based on the patient's cardiovascular fitness. Patients with improved cardiovascular fitness can proceed to "harder" activities, achieving heart rates exceeding 70% of maximum.
   3. Duration: 30 minutes, preceded and followed by stretching and flexibility exercises for a minimum of 5–10 minutes.
   4. Frequency: at least 3 days per week. Results are best if exercise occurs nearly every day.
   5. Avoid strenuous exercise if fasting glucose levels are ≥250 mg/dL. Avoid all forms of exercise if glucose levels are ≥300 mg/dL and/or ketosis is present.
   6. Monitor blood glucose before, during, and after exercise, to learn responses to different exercise conditions and to identify when changes in insulin and/or food intake are necessary.
   7. Consume added foods as needed to avoid hypoglycemia. A rapidly-absorbed carbohydrate source should be readily available during exercise and for up to 8 hours after exercise is completed.

*Exercise limitations are imposed by preexisting coronary or peripheral vascular disease, proliferative retinopathy, peripheral or autonomic neuropathy, and/or poor glycemic control.

LDL = low-density lipoprotein.

TYPE 2 DIABETES

Nonpharmacologic Measures

In many type 2 diabetic patients, diet and exercise are the only therapeutic interventions required to restore metabolic control. As a result, the temptation to use pharmacologic agents should be restrained at the outset, unless the patient is symptomatic or hyperglycemia is severe. On the other hand, the clinician must also resist the temptation to be satisfied by the elimination of symptoms, which is simply the first of many steps in the comprehensive treatment of diabetes. The combination of lifestyle changes and medications can reduce both cardiovascular and microvascular events by about 50%.

DIET. Irrespective of initial weight, modest weight reduction (on the order of 5 kg) in obese diabetic patients leads to improved glycemic control. The dramatic impact of weight loss is mediated by changes in insulin-responsive tissues, as well as by enhanced β-cell activity; insulin resistance diminishes, glucose production declines, and

lower glucose levels improve glucose-stimulated insulin secretion. The beneficial effects of weight loss are not restricted to glucose; dietary therapy also yields improved lipid profiles and reductions in systemic blood pressure. In general, it matters little how weight loss is achieved, provided that good health is preserved and adequate nutrition is maintained. Successful weight loss is best achieved by the combination of a supportive environment that emphasizes long-term goals, regular exercise to increase energy expenditure, and long-term behavior modification.

In sedentary diabetic patients, maintenance caloric requirements can be as low as 20 to 25 kcal per kilogram of body weight per day. In these individuals, the classically prescribed 1800-kcal diet will be ineffective in producing weight loss. It is sensible to begin with a nutritionally sound, individually tailored diet that is aimed at producing a caloric deficit of about 500 kcal per day. Because a caloric deficit of approximately 3500 kcal is required to lose 1 lb of body fat, weight loss using this method can be expected at 1 lb per week. For obese patients with a history of multiple failed weight loss attempts, very low calorie diets (<1000 kcal/day) can be useful when carried out under medical supervision. Orlistat, a gastrointestinal lipase inhibitor that reduces dietary fat absorption, can be an effective adjunct for achieving weight loss in some patients; it may also improve glycemic control and lipoprotein profiles. Regardless of the method used, experience tells us that most patients are unable to maintain low-calorie diets for an extended period of time; if successful, the majority of patients regain lost weight. In patients with type 2 diabetes, metabolic factors may also contribute to difficulty maintaining weight loss. Dieting reduces glycosuria and therefore lessens urinary caloric loss. Also, the expected decrease in basal metabolic rate during weight loss is accentuated in diabetic patients, because weight loss reverses both accelerated gluconeogenesis and the futile cycling of substrates; these conditions, commonly seen in poorly controlled diabetes, waste a good deal of energy in the hyperglycemic state.

Even when diabetic patients cannot lose weight, a careful meal plan is a valuable tool for reducing their risk of cardiovascular disease. This benefit is best achieved by restricting saturated fats and cholesterol and by raising the dietary content of carbohydrates and monounsaturated fats. It was originally thought that carbohydrate intake should be restricted in diabetes; however, it is now appreciated that a diet high in carbohydrate (>50%) may improve insulin action and glycemic control, particularly in patients with mild hyperglycemia. In patients with more severe fasting hyperglycemia or with triglyceride elevations aggravated by high-carbohydrate diets, reduced carbohydrate intake (<45% of total calories) and greater reliance on monounsaturated fats may be preferable. It has also been assumed that carbohydrate intake should be focused on complex carbohydrates (starches), and that sucrose should be avoided; however, evidence supporting these assumptions is scarce. Simple sugars appear to raise glucose levels to a similar extent as complex carbohydrates; thus, total carbohydrate intake, rather than type of carbohydrate, should be the primary consideration. Fiber-containing carbohydrates such as oats, gums, legumes, and fruit pectin may also be beneficial, since fiber blunts meal-induced glucose excursions by delaying gastric emptying and carbohydrate absorption. Fiber helps to prevent constipation and may also contribute to lowering of triglyceride and low-density lipoprotein (LDL) cholesterol levels.

Another key component of the diabetic meal plan is to alter patterns of dietary fat. The typical Western diet, high in saturated animal fat, likely contributes to the development of atherosclerosis. Diabetic patients with normal lipid profiles are encouraged to follow the recommendations of the National Cholesterol Education Program (NCEP) by limiting total fat intake to less than 30% of total calories, with less than 10% of calories as saturated fat and less than 300 mg/day of dietary cholesterol (see Table 242–6). If low-density lipoprotein levels are elevated, stricter recommendations apply (NCEP Step II diet), with less than 7% of calories as saturated fat and less than 200 mg/day of dietary cholesterol. As mentioned earlier, if elevated triglycerides are of concern, one should consider a moderate *increase* in monounsaturated fats, to replace dietary carbohydrates; of course, increasing fat intake should always be recommended with caution in patients with obesity. Despite a lack of supporting scientific evidence, moderation of dietary protein is also currently recommended for patients with diabetes; this issue assumes greater importance in patients with proteinuria and overt diabetic nephropathy.

EXERCISE. Regular exercise is a powerful adjunct in the treatment of type 2 diabetes. Long-term studies demonstrate consistent beneficial effects of regular exercise on carbohydrate metabolism and insulin sensitivity, which can be maintained for several years. Exercise also facilitates weight loss and its maintenance, which further improves glycemic control and also has beneficial effects on cardiovascular risk: regular exercise lowers triglyceride-rich very low density lipoprotein levels, raises high-density lipoprotein levels, and improves fibrinolytic activity. In general, "moderate" levels of exercise should be prescribed most days of the week (see Table 242–6). Limitations may be imposed by preexisting coronary or peripheral vascular disease, proliferative retinopathy, peripheral or autonomic neuropathy, and poor glycemic control.

Pharmacologic Intervention

ORAL GLUCOSE-LOWERING AGENTS. The hypoglycemic effect of sulfonylureas was first noted in the 1940s, during the development of sulfa antibiotics. Chlorpropamide, the first oral agent approved for use in the United States, was released in 1954. With the exception of phenformin (which was briefly available before being pulled from the market in the 1970s), sulfonylureas were the only oral agents available in the United States for more than 40 years. In contrast, since the 1995 approval of metformin by the FDA, several new classes of oral agents have become available for the treatment of type 2 diabetes (Table 242–7 and Fig. 242–8). Oral agents are indicated in patients in whom diet and exercise fail to achieve treatment goals and may be favored over insulin in older patients with relatively mild degrees of hyperglycemia. Patients with more severe hyperglycemia generally require insulin during the initial phases of treatment; once glucose levels have stabilized and the "toxic" effects of severe hyperglycemia on β-cell function and insulin action have been minimized, many of these patients can then be converted to oral agents.

Sulfonylureas. Sulfonylureas are insulin "secretagogues," which act through specific sulfonylurea receptors on the β-cell surface. Drug-receptor binding acts to close adenosine triphosphate–dependent potassium channels, resulting in cellular depolarization, calcium influx, and the translocation of insulin secretory granules to the β-cell surface. The resulting release of insulin into the portal vein rapidly suppresses hepatic glucose production, and later facilitates peripheral glucose utilization; insulin resistance commonly diminishes as a result of the reversal of glucotoxicity. Because sulfonylureas rely on a preserved β-cell response, they are ineffective in the treatment of type 1 diabetes.

Although the sulfonylureas differ in relative potency, effective dosage, metabolism, and duration of action, from a clinical standpoint these differences have marginal significance (see Table 242–7). Each drug has similar hypoglycemic effects: at maximally effective doses, an average drop in hemoglobin A_{1c} of 1 to 2% is expected, corrdelating to average fasting plasma glucose reductions of 40 to 80 mg/dL. Drugs with hepatic metabolism and a shorter duration of action have

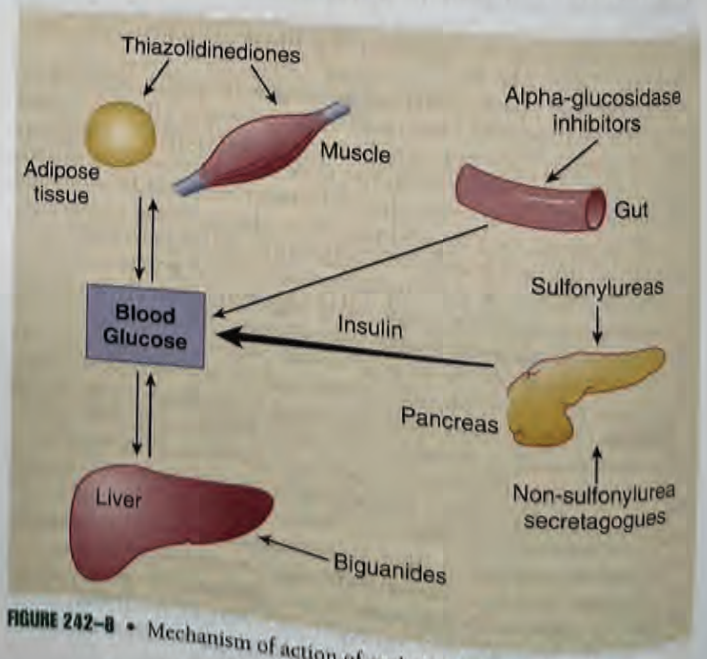

FIGURE 242–8 • Mechanism of action of oral glucose-lowering agents.

Table 242–7 • CHARACTERISTICS OF ORAL GLUCOSE–LOWERING AGENTS

CLASS/AGENT	ACTION	ADMINISTRATION	TOTAL DAILY DOSE (MG/D)	DOSES/ DAY	METABOLISM AND EXCRETION	DURATION OF ACTION (HRS)	PRINCIPLE SIDE EFFECTS
Sulfonylureas	Insulin secretagogues	30 minutes prior to meals					Hypoglycemia, weight gain, hyperinsulinemia
First generation							
Chlorpropamide			100–500	1	K > L	~60	
Tolazamide			100–1000	1–2	L > K	12–24	
Tolbutamide			500–3000	2–3	L > K	6–12	
Second generation							
Glimepiride			1–8	1	L > K	24	
Glyburide			1.25–20	1–2	L > K	Up to 24	
Glyburide micronized			1.5–12	1–2	L > K	Up to 24	
Glipizide			5–40	1–2	L > K	Up to 24	
Glipizide GITS			5–20	1	L > K	24	
Biguanide	Inhibits hepatic gluconeogenesis	With meals					Gastrointestinal disturbances (abdominal pain, nausea, diarrhea), lactic acidosis
Metformin			500–2550	2–3	K	Up to 24	
Metformin XR			500–2000	1	K	24	
Metformin/ Glyburide			1.25–20/ 250–2000	2	K/L > K	Up to 24	
Thiazolidinediones	Insulin sensitizers (PPAR-γ agonists)	With meals					Fluid retention, weight gain, congestive heart failure, edema, anemia. Due to the troglitazone experience, periodic monitoring of LFTs is recommended
Pioglitazone			15–45	1	L	24	
Rosiglitazone			4–8	1–2	L	Up to 24	
Alpha-glucosidase inhibitors	Delay carbohydrate absorption	Just prior to meals					Gastrointestinal disturbances (abdominal pain, nausea, diarrhea),? LFT elevation
Acarbose			75–300	3	Gut/K*	Local effect	
Miglitol			75–300	3	K	Local effect	
Non-sulfonylurea secretagogues	Insulin secretagogues	15 minutes prior to meals					Hypoglycemia, weight gain, hyperinsulinemia
Repaglinide			1.5–16	3	L > K	<4	
Nateglinide			180–360	3	K > L	<4	

*The small fraction (<2%) of acarbose that is absorbed is eliminated by the kidneys.
K = kidney; L = liver; LFT = liver function test.

advantages in elderly patients with impaired renal function (who are more vulnerable to hypoglycemia) but may be less effective in practice because of noncompliance with multiple dosing schedules. Conversely, longer-acting agents can be dosed once daily, enhancing compliance but increasing the risk of prolonged hypoglycemia. After the appropriate drug is chosen, treatment is initiated at low doses, with dose increases every 1 to 2 weeks until either treatment goals are met or "maximally effective" doses are reached. Note that for all sulfonylureas, efficacy plateaus at about 50% of the listed maximum dose; above these "maximally effective" doses, there is little clinical benefit derived from dose escalation, and alternative therapies should be considered.

The majority of type 2 patients initially respond to sulfonylureas with improved glycemic control. However, 10 to 20% of patients show little or no response; these cases are known as "primary" drug failures. Additionally, many other patients will experience the loss of drug effect after years of successful therapy; these "secondary" drug failures occur at rates of 5 to 10% per year, because of progressive β-cell failure, drug tolerance, lack of enthusiasm for diet and exercise, and/or the superimposition of comorbid illness. Glucotoxicity itself can also contribute to worsening glucose control. In clinical practice, early signs of secondary drug failure should provoke renewed attempts to reinforce diet and exercise, as well as a reassessment of drug dosage. The re-appearance of hyperglycemia despite maximally effective drug doses signals the need to add another class of oral agent, or to institute insulin therapy. Overall, only approximately 25% of patients reach glucose targets with a sulfonylurea alone; stated another way, three in four patients will require additional modes of therapy.

Advantages of sulfonylureas include low cost (especially with generics), convenience (once-daily dosing), and the proven reduction of microvascular endpoints (retinopathy, nephropathy, and probably neuropathy) in the UKPDS. Disadvantages include hypoglycemia, weight gain, and the theoretical acceleration of so-called "β-cell exhaustion."

Non-sulfonylurea Secretagogues. Repaglinide, a non-sulfonylurea that interacts with a different portion of the sulfonylurea receptor to stimulate insulin secretion, was approved by the FDA in 1998. A similar agent, nateglinide, was released 2 years later. The major advantage of the nonsulfonylurea secretagogues over sulfonylureas is their rapid and relatively short duration of action, which may attenuate postprandial glucose excursions and reduce the risk of fasting hypoglycemia. Both drugs require frequent daily dosing and should be taken 0 to 15 minutes before meals. Repaglinide and nateglinide exhibit similar or diminished glucose-lowering power compared with the sulfonylureas. Both agents have a favorable side effect profile and typically produce less clinical hypoglycemia than traditional sulfonylureas. The primary disadvantages of the nonsulfonylurea secretagogues are their higher cost and multiple dosing schedules.

Biguanides. Metformin is the only biguanide available for use in the United States. Unlike sulfonylureas, this agent is an "insulin

sensitizer," which acts mainly to reduce hepatic glucose production by suppressing gluconeogenesis. Metformin may also augment peripheral glucose utilization, although this effect may be secondary to reversal of glucotoxicity. Metformin exhibits a similar glucose-lowering effect to the sulfonylureas, with expected hemoglobin A_{1C} reductions of 1 to 2%. Metformin has a relatively short half-life (it is eliminated exclusively by the kidney) and is therefore given in two or three divided doses with meals. An extended-release metformin product, released in 2001, allows for more convenient daily dosing.

Because the effects of metformin are extrapancreatic, insulin levels generally fall, a potential advantage if the theory implicating hyperinsulinemia in the development of atherosclerosis proves correct. Other advantages of metformin include mild weight loss, mild (<10%) low-density lipoprotein and triglyceride reductions, and little induced hypoglycemia. Side effects are primarily gastrointestinal, including abdominal pain, bloating, nausea, diarrhea, and anorexia; these may be partially responsible for the weight loss effect. Metformin can also rarely produce lactic acidosis (approximately 0.03 cases per 1000 patient years) and should therefore not be given to patients with renal insufficiency (serum creatinine ≥1.5 in males or ≥1.4 in females), liver disease, congestive heart failure, metabolic acidosis, or a history of alcohol abuse. The drug should also be held in dehydrated patients, and for 48 to 72 hours prior to either surgery or the administration of intravenous radiocontrast agents.

With regard to evidence-based medicine, metformin has the most proven track record among the oral agents. Like sulfonylureas, metformin reduced microvascular end points in the UKPDS; unlike sulfonylureas, it may also have produced reductions in myocardial infarction, diabetes-related death, and overall mortality. Furthermore, in the recently released results of Diabetes Prevention Program (see below), metformin showed an ability to delay the progression to diabetes in patients with impaired glucose tolerance.

Thiazolidinediones. Thiazolidinediones (TZDs) reduce insulin resistance, most likely through activation of PPAR-γ (peroxisome proliferator-activated receptor gamma), a nuclear receptor that regulates the transcription of several insulin-responsive genes that regulate carbohydrate and lipid metabolism. The biologic effect of TZDs is principally mediated by stimulation of peripheral glucose metabolism. PPAR-γ activation also reduces lipolysis and enhances peripheral adipocyte differentiation, thereby redistributing fat stores from the liver, muscle and visceral depots to subcutaneous depots, an effect that likely contributes to the "insulin-sensitizing" effects of the TZDs. In 1997, troglitazone was the first TZD approved for use in the United States; although effective, the drug was withdrawn from the market in 1999 because of concerns over idiosyncratic hepatotoxicity. Two new TZDs, rosiglitazone and pioglitazone, were FDA-approved in 1999; these agents have negligible hepatotoxicity and are currently in widespread use.

Used as monotherapy, TZDs have slightly milder (and more slowly developing) glucose-lowering effects as compared with sulfonylureas and metformin, with expected hemoglobin A_{1C} reductions of 1.0 to 1.5%. Clinical advantages of TZDs include convenience (once-daily dosing), little hypoglycemia, and reduced levels of circulating insulin. TZDs have many other beneficial effects, including (1) lower triglyceride levels (particularly with pioglitazone), (2) higher high-density lipoprotein levels, (3) reductions in small, dense low-density lipoprotein cholesterol, (4) small reductions in blood pressure, (5) improved endothelial function, and (6) enhanced fibrinolytic activity. Studies suggest that TZDs may also slow the growth of atherosclerotic plaque in carotid arteries; ongoing clinical trials are investigating their use in cardiovascular risk reduction. Finally, there is some evidence that TZDs may also slow the decline of β-cell function, thus delaying the clinical progression from impaired glucose tolerance to overt diabetes mellitus.

Compared to other oral hypoglycemic agents, TZDs are more costly. Side effects of the TZDs are largely related to fluid retention and fat redistribution and include weight gain, edema, mild anemia, and worsening of congestive heart failure. These drugs are therefore not recommended for use in patients with moderate-to-severe congestive heart failure or those with severe anemia. As mentioned earlier, the two newer agents appear to be relatively free of hepatic toxicity; however, because of the troglitazone experience, they should not be used in patients with active liver disease or with elevated serum transaminases (ALT ≥2.5 times the upper limit of normal). The manufacturers of both rosiglitazone and pioglitazone currently recommend monitoring liver function tests every 2 months during the first year of therapy, with "periodic" testing thereafter. TZDs should be discontinued if transaminases are three or more times the upper limit of normal.

α-GLUCOSIDASE INHIBITORS. Acarbose and miglitol are competitive inhibitors of α-glucosidases, brush-border enzymes in the proximal small intestine that serve to break down complex carbohydrates into monosaccharides. These agents delay the absorption of carbohydrates such as starch, sucrose, and maltose but do not affect the absorption of glucose and other monosaccharides. To be effective, acarbose and miglitol must be taken at the beginning of each carbohydrate-containing meal, usually three to four times per day. Acarbose is minimally absorbed systemically, while miglitol is absorbed and rapidly excreted (unchanged) in the urine. Perhaps as a result of improved glycemic control, both of these agents are associated with modest (<10%) reductions in circulating triglyceride levels and have no appreciable effects on low-density or high-density lipoprotein cholesterol.

In controlled trials performed in patients with type 2 diabetes, α-glucosidase inhibitors reduced postprandial glucose excursions and produced small (0.5 to 1.0%) but meaningful reductions in hemoglobin A_{1C}. The most common side effects associated with both acarbose and miglitol are abdominal pain, bloating, flatulence, and diarrhea; these adverse events can be minimized by initiating therapy at low doses and by using a slowly escalating dose titration schedule. Still, the manufacturers of both drugs discourage their use in patients with inflammatory bowel disease, colonic ulceration, or any other significant chronic gastrointestinal disorder.

INSULIN THERAPY. Insulin is commonly used as first-line therapy for nonobese, younger, or severely hyperglycemic patients with type 2 diabetes and is often temporarily required during times of severe stress (e.g., injury, infection, surgery) or during pregnancy. Insulin should not be used as a first-line therapy for patients who are poorly compliant, unwilling to self-monitor glucose levels, or at high risk for hypoglycemia (e.g., the very elderly). In obese patients, profound insulin resistance often necessitates the use of large doses of insulin, which can interfere with efforts to restrict caloric intake and achieve weight loss. In leaner patients, and in patients with relatively mild fasting hyperglycemia (who continue to maintain endogenous insulin secretory capacity), relatively small doses of basal insulin (e.g., 0.3 to 0.4 U/kg of body weight per day) given once or twice per day may be sufficient to achieve glucose targets. Many of these patients retain some degree of meal-stimulated endogenous insulin secretion and may therefore require less rapid-acting insulin as well.

Although it is common practice to administer a single dose of intermediate-acting insulin in the morning, the glucose-lowering effect of this regimen does not usually extend over a full 24-hour period. Because a key element of successful insulin treatment is to counteract accelerated rates of endogenous glucose production in the morning, it is generally more effective to split the dose and administer sufficient amounts of intermediate-acting insulin in the evening (preferably at bedtime) to optimize control. Alternatively, a single dose of intermediate-acting insulin given at bedtime or of insulin glargine may be effective throughout the following day in patients who have retained the capacity to secrete insulin with meals. This approach has the advantage of greater simplicity and compliance and can be combined with oral glucose-lowering agents during the day to facilitate endogenous insulin release and action.

With regard to the *initiation* of insulin therapy, there are many acceptable approaches. As a first step, the total daily dose of insulin should be estimated from body weight; total insulin requirements typically range between 0.5 and 1.0 U/kg/day. One classic method for starting insulin is to divide the total daily dose unevenly, with two thirds given before breakfast and the remaining one third before dinner. Each of the two doses is then further subdivided: at breakfast, two thirds of the dose is given as intermediate-acting insulin and the other one third as a rapid-acting preparation, while at dinner, the dose is divided into two equal parts. As an example, for a 90 kg man with estimated requirements of 0.67 U/kg/day, 60 U of insulin may be required. Using the above method, this patient might receive 27 units of NPH with 13 units of regular insulin before breakfast, then 10 units of NPH with 10 units of regular insulin before dinner. Please note that this is only one of many "rule-of-thumb" methods for the initiation of insulin; with the advent of intensive therapy, such methods have become largely obsolete. Furthermore, in the absence of hyperglycemic symptoms, clinicians should generally begin with more conservative doses of insulin, to minimize hypoglycemia and to smooth the patient's transition to subcutaneous insulin therapy.

In clinical practice, most insulin-treated patients are obese, have more severe hyperglycemia, and have already failed oral therapy. Such patients have higher degrees of both insulin deficiency and insulin resistance; as a result, they may require multiple-dose insulin regimens similar to those of type 1 patients. In these patients, it is best to distribute the insulin as evenly as possible throughout the day and to provide sufficient coverage overnight to control fasting hyperglycemia. The complexity of the regimen should be individualized according to the clinical context, the patient's ability to perform self-care, and most importantly, the patient's level of education and motivation.

In many cases, the combination of intensive insulin therapy with oral hypoglycemic agents (TZDs or metformin) may reduce insulin dose requirements and improve glycemic control. While growing in acceptance, the potential benefit of reducing circulating insulin levels (using combination therapy) on the development of atherogenesis remains to be established. Experience with the use of intensified insulin treatment, including continuous subcutaneous insulin infusion pumps and multiple subcutaneous injection regimens, is growing in patients with type 2 diabetes. Preliminary results suggest that intensified treatment may be successfully applied to many of these patients.

Treatment Strategies for Type 2 Diabetes

In contrast to type 1 diabetes, in which insulin therapy is required, several pharmacologic options exist for the management of type 2 diabetes. The pros and cons of the various oral hypoglycemic agents have already been discussed; often, it is difficult to justify the use of one oral agent over another. In the literature, many studies have compared the glucose-lowering power of one oral agent to another; however, few studies have compared the drugs in terms of relevant clinical outcomes such as mortality, cardiovascular disease, or microvascular complications. To date, the largest study to address such outcomes in type 2 diabetes was the UKPDS.

In the UKPDS, improved outcomes produced by intensified therapy were similar for patients given insulin, sulfonylureas, or metformin therapy. The ability of the study to detect differences among the various treatments was limited because of drug crossovers and because of the frequent need for drug combinations as the study progressed. The use of metformin in the UKPDS deserves specific mention here because of conflicting results. In the study, patients initially assigned to metformin therapy showed decreased rates of microvascular complications, combined diabetes-related end points, diabetes-related deaths, all-cause deaths, and myocardial infarction as compared with conventionally treated patients; in contrast, patients treated with insulin or sulfonylureas demonstrated reductions in only two of the five categories: microvascular complications and combined diabetes-related end points. Thus, metformin therapy appeared advantageous. Late in the study, however, 537 patients failing sulfonylurea therapy were randomly assigned to either continue the sulfonylurea alone or to add metformin. Compared to the sulfonylurea subgroup, this combined-therapy subgroup had an unexpected 60% *increase* in all-cause mortality. The results of this "substudy" have been called into question, since it was unblinded and lacked a placebo control. In addition, 25% of the patients assigned to continue monotherapy eventually required metformin to achieve glucose targets. In summary, based on the UKPDS, it is difficult to offer an unequivocal recommendation for metformin as compared to sulfonylureas or insulin therapy.

The choice of initial pharmacologic therapy for type 2 diabetes should be influenced mainly by the severity of fasting hyperglycemia, the degree of obesity, and the presence and magnitude of hyperglycemic symptoms. Other factors such as age, education, motivation, and comorbid conditions should also be considered. To determine the effectiveness of the therapy selected, drug regimens should be adjusted over a 3-month period based on glucose self-monitoring; failure to meet glucose targets within 3 months suggests the need for combination therapy (Fig. 242–9). Published clinical trials comparing drug combinations to monotherapy have generally shown additive reductions in hemoglobin A_{1c}; with few exceptions, the magnitude of A_{1c} reduction is similar to that achieved when the added agent is used as monotherapy. As is the case with monotherapy, there is no convincing evidence favoring one combination regimen over another, and most combinations have been approved by the FDA. "Triple-therapy," or combining three agents to achieve glucose targets, is also used frequently in clinical practice (although not yet with FDA approval) and appears to be effective. Ultimately, if glucose targets cannot be met by combining oral agents, insulin remains an effective treatment option.

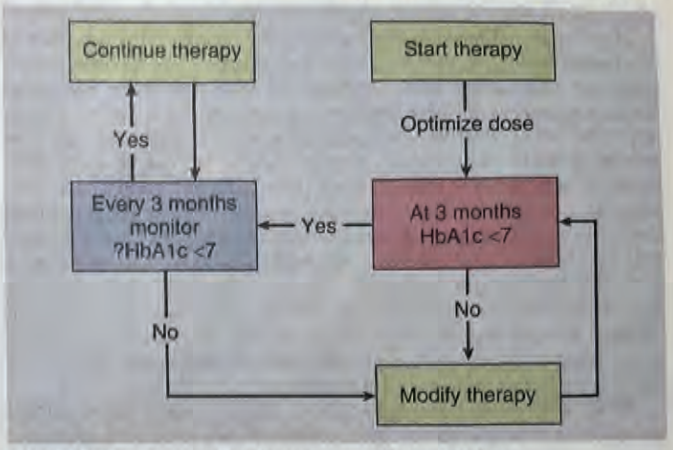

FIGURE 242–9 • Strategy for the treatment of type 2 diabetes.

MONITORING

SELF-MONITORING OF BLOOD GLUCOSE. Self-monitoring of blood glucose has revolutionized the management of diabetes. It actively involves patients in the treatment process, allows more rapid treatment adjustments, and reinforces dietary changes. Self-monitoring provides the patient with the tools necessary to assist in managing their disease and is especially useful during periods of stress and for patients who are susceptible to hypoglycemia. Urine glucose testing is unreliable and should not be used.

Newer glucose meters are small, portable, and reliable, give a digital readout, and have computerized memory to facilitate record keeping. Blood sampling is facilitated (and made less painful) by automated, spring-operated lancet devices; recent "off-the-finger" products also allow for more comfortable testing. Self-monitoring of blood glucose is of maximal value if the patient performs tests on a regular basis, can accurately measure glucose levels, and can make use of the results. The patient must become familiar with what a normal glucose value is, what the glucose targets are, and how levels can vary with changes in diet, activity, and insulin absorption. For most insulin-dependent patients, day-to-day adjustments in short-acting insulin based on pre-meal values and a "sliding scale" can be readily accomplished. These patients also need to examine the effects of their longer-acting insulin injections, and to make adjustments if glucose levels (e.g., pre-breakfast, pre-dinner, and bedtime values) are not within the target range. At a minimum, patients should be able to adjust to repetitive patterns of hypoglycemia or hyperglycemia, as well as to periods of stress and illness ("sick days"). For patients in the latter circumstance, urine testing for ketones should also be routinely performed.

The success of insulin therapy depends on the frequency with which the patient performs self-monitoring. Patients with type 1 diabetes should be encouraged to monitor before each meal and at bedtime and whenever symptoms occur. Periodic checks 90 to 120 minutes after meals help to control postprandial hyperglycemia, and patients should occasionally monitor pre-dawn (e.g., 3 AM) glucose levels to avoid nocturnal dips. Currently, no clear guidelines have been established regarding the frequency of blood glucose monitoring for type 2 diabetes. Type 2 patients who are treated with insulin should self-test daily, usually before breakfast, before dinner, and at bedtime. The frequency of blood glucose self-monitoring will depend largely on the stability of metabolic control; testing should be more frequent during the initiation of treatment, after changes in therapy, and during all times that altered metabolic control is suspected. Type 2 patients maintained on dietary therapy should, at the very least, learn self-monitoring of blood glucose to prevent metabolic decompensation. These patients also benefit from periodically monitoring glucose levels so that they may better appreciate how changes in their diet can adversely affect glycemic control.

CONTINUOUS GLUCOSE MONITORING. Traditional self-monitoring of blood glucose is often inadequate to optimize metabolic control.

Continuous glucose monitoring reveals that tight glycemic control is often being achieved at the expense of unacceptably high rates of nocturnal hypoglycemia and also that postprandial glucose excursions are often larger than expected. To minimize these highs and lows, continuous glucose monitoring systems have recently been approved for clinical use. A currently available "real-time" glucose sensor is worn "Holter-style" over a 72-hour period, to alert clinicians to previously undetected nocturnal hypoglycemia and postprandial glucose elevations. Another system worn on the wrist uses iontophoresis to measure interstitial glucose levels at frequent intervals. It is hoped that armed with this additional information, patients and clinicians can then adjust the therapeutic regimen to minimize glucose excursions and maximize patient safety. Undoubtedly, continuous glucose monitoring methods as they become more reliable and convenient will eventually replace episodic self-monitoring, especially for patients with type 1 diabetes.

GLYCOHEMOGLOBIN. Glycohemoglobin (glycosylated hemoglobin) assays have emerged as the "gold standard" for long-term glycemic control. The test does not rely on a patient's ability to self-monitor blood glucose levels and is not influenced by acute glycemic changes or by recent meals. Glycohemoglobin is formed when glucose reacts nonenzymatically with the hemoglobin A molecule; it is composed of several fractions, the largest being hemoglobin A_{1C}. Hemoglobin A_{1C} (expressed as the percentage of total hemoglobin) varies in proportion to the average level of glucose over the lifespan of the red blood cell, thereby providing an index of glycemic control during the preceding 6 to 12 weeks. Several assay methods have been developed that yield different ranges for nondiabetic control subjects; clinicians should therefore become familiar with the specific assays used for testing their patients.

Although ambient glucose levels are the dominant influence on glycohemoglobin levels, other factors can confound the interpretation of the test. For example, any condition that increases red blood cell turnover (e.g., pregnancy, hemolytic anemia) spuriously lowers glycohemoglobin levels, regardless of the assay used. Some assays yield spuriously low values in patients with hemoglobinopathies (e.g., sickle cell disease or trait, hemoglobin C or D), or high values when either hemoglobin F is increased (e.g., thalassemia, myeloproliferative disorders) or when large doses of aspirin are consumed. Thus, for unexpectedly high or low values encountered in clinical practice, factors that alter the specific assay should be excluded. In most cases, discrepancies between self-monitoring of blood glucose and glycohemoglobin results reflect problems with the former rather than the latter. Although glycohemoglobin provides the most accurate estimate of overall glycemic control, it has limited value in guiding specific changes in therapy; in clinical practice, frequent blood glucose measurements are essential to properly adjust the therapeutic regimen.

MANAGEMENT PLAN/TREATMENT GOALS. A management plan should take into consideration the life patterns, age, work and school schedules, psychosocial needs, educational level, and motivation of each individual patient. The plan should include lifestyle changes, a meal plan, medications, monitoring instructions (including "sick day" management), and education regarding the prevention and treatment of hypoglycemia. Importantly, all components of the plan must be both understood and accepted by the patient. Active patient participation in problem solving, as well as ongoing support from a health care team, is critical for the successful management of diabetes. At each visit, the management plan should be reviewed, and an assessment should be made of the patient's progress in achieving glucose targets; if goals are not being met, causes need to be identified, and the plan should then be modified accordingly. At each visit, the history and physical examination should focus on early signs and symptoms of retinal, cardiovascular, neurologic, and podiatric complications, and on reinforcement of the diet and exercise prescription. A complete ophthalmologic examination, assessment of cardiovascular risk factors, and measurement of urinary albumin excretion (through either a timed collection or two "spot" urine albumin-to-creatinine ratios) should all be performed annually. Specialized podiatric care is also recommended for all patients with evidence of pedal neuropathy.

Formulation of individual glycemic goals must take into account the results of the DCCT (type 1 diabetes) and the UKPDS (type 2 diabetes) in the context of the patient's capacity to implement the treatment plan, risk for hypoglycemia, and other factors that would alter the risk-benefit ratio. Table 242–8 presents target glycemic guidelines for nonpregnant diabetic patients as well as targets for other clinical factors (e.g., blood pressure, lipids) that increase the potential for diabetic complications.

Table 242–8 • THERAPEUTIC TARGETS FOR NONPREGNANT DIABETIC PATIENTS

PARAMETERS	NORMAL	TARGET*	INTERVENTION SUGGESTED†
Preprandial plasma glucose (mg/dL)	<110	80–120	<80 or >140
2-hour postprandial glucose (mg/dL)	<140	<160	>180
Bedtime plasma glucose (mg/dL)	<120	100–140	<100 or >160
Hemoglobin A_{1c} (%)	<6	<7‡	>7
Low-density lipoprotein cholesterol (mg/dL)	<130	<100	>100
High-density lipoprotein cholesterol (mg/dL)	>40	>45 (men), >55 (women)	<40
Fasting triglycerides (mg/dL)	<150	<150	>150
Blood pressure (mg Hg)	<140/90	<130/85	>130/85

*Clinical targets vary for individual patients, depending on assessment of overall health and risk-to-benefit ratio.

†Interventions may include dietary therapy, exercise prescription, and/or pharmacologic intervention.

‡Hemoglobin A_{1c} control to <6.5% is advocated by some authorities, especially in type 2 diabetics.

PANCREAS TRANSPLANTATION

Intensive insulin therapy rarely (if ever) restores glucose homeostasis to levels achieved in nondiabetic individuals. As a result, the search for more effective methods of treatment remains a crucial long-term goal of diabetes research. Pancreas transplantation is promising in this regard; with growing experience in recent years, there have been substantial improvements in the outcome of pancreas transplant surgery. In major centers, 80 to 90% of patients emerge from the perioperative period with a functioning graft; once insulin independence is established, the majority of patients remain stable for several years. Successful pancreas transplantation improves the quality of life of patients with diabetes, primarily by eliminating the need for dietary restrictions, insulin injections, and frequent glucose self-monitoring. Although pancreas transplantation is only partially able to reverse long-term diabetic complications, it effectively eliminates acute complications such as hypoglycemia and diabetic ketoacidosis.

Unfortunately, because of the need for long-term immunosuppression, pancreas transplantation is at present an option for only a select group of patients, mainly for type 1 diabetics who will already require immunosuppression for a renal allograft. In such individuals, successful pancreas transplantation is also effective in preventing nephropathy in the grafted kidney. In the absence of indications for a kidney transplant, pancreas transplantation should generally be considered only in diabetic patients with a history of frequent, severe metabolic complications (e.g., hypoglycemia, ketoacidosis), in whom insulin therapy consistently fails to achieve metabolic control.

Pancreatic islet cell transplantation holds many potential advantages over the whole-gland transplant, since it is simpler to perform and less costly. Until recently, islet transplantation has had disappointing results with regard to long-term insulin independence; however, a recent series published out of Edmonton, Alberta, Canada, suggests that outcomes may be improving and that islet transplantation may become a therapeutic option. In this 12-patient series (median follow-up, 10 months), 4 patients had normal glucose tolerance, 5 had IGT, and 3 had a stable diabetes characterized by endogenous insulin production and a low risk of hypoglycemia. Interestingly, compared with diabetic patients, islet-cell transplantation has been easier in patients with chronic pancreatitis, many of whom have successfully undergone total pancreatectomy followed by intraportal injection of pancreatic islets. The implication here is that with diabetes, the use of immunosuppressive drugs, chronic low-grade rejection of the foreign islet grafts, and/or the activation of an autoimmune response may account for transplant failure. If these inferences are correct, the

future of islet transplantation therapy for diabetes depends mainly on manipulating the islet and/or the immune response and the availability of donor islets, rather than on technical surgical advances.

Prevention of Diabetes

As the pathogenesis of both types of diabetes becomes better understood, the potential for prevention of these diseases is more realistic. Two large, multicenter disease prevention trials have already been completed in the United States, and several more are planned.

In the Diabetes Prevention Program, more than 3000 overweight subjects with IGT were randomized into four treatment arms: (1) intensive lifestyle changes aimed at reducing body weight by 7% through a low-fat diet and 150 minutes of weekly exercise; (2) treatment with metformin, 850 mg twice per day; (3) treatment with placebo pills, twice per day; and (4) treatment with troglitazone, 400 mg once per day (this arm was discontinued because of concerns over liver toxicity). The latter three groups also received standard information regarding diet and exercise. On the advice of the Diabetes Prevention Program's external data monitoring board, the trial was stopped a year early because of definitive results: 29% of patients in the placebo group developed diabetes during the average follow-up period of 3 years, compared with 22% of patients taking metformin and only 14% of patients undergoing intensive diet and exercise.[4] Put another way, patients taking metformin reduced their risk of diabetes by 31% versus standard care, whereas patients undergoing intensive lifestyle interventions reduced their risk by an impressive 58%. This suggests that patients with IGT (more than 20 million patients in the United States alone, according to recent estimates) can sharply lower their immediate risk of diabetes with intensive lifestyle changes (or in some cases with metformin), and puts the onus on clinicians to screen, identify, and appropriately treat patients with IGT. Postmenopausal estrogen and progestin can reduce the incidence of type 2 diabetes by 35%,[5] but the adverse effects of such therapy may outweigh its benefits (Chapter 256).

Results of the Diabetes Prevention Trial Type 1 have also been recently published. In this study, "high-risk" relatives of type 1 diabetic subjects (based on antibody screening and HLA typing) were randomly assigned to no treatment or to low-dose insulin injections, a therapy used successfully in rodent models of spontaneous autoimmune diabetes to prevent disease expression. After 5 years of observation, nearly 60% of these "high-risk" patients developed diabetes, as predicted by clinical models; unfortunately, there was *no* difference in incidence between the insulin and no treatment arms.[6] Another substudy of the Diabetes Prevention Trial Type 1, testing the prevention of diabetes using *oral* insulin in patients at more moderate risk for disease, is still underway. Other putative preventive strategies are also under investigation.

ACUTE METABOLIC COMPLICATIONS

HYPERGLYCEMIC STATES

Metabolic decompensation in diabetes is generally classified into one of two broad clinical syndromes: diabetic ketoacidosis (DKA) or the hyperosmolar hyperglycemic state (HHS). Although DKA is generally seen in type 1 patients and the HHS affects type 2 patients, lines of classification are commonly blurred; for example, the HHS can present with variable degrees of ketosis and acidosis, while DKA is being seen with increasing frequency in obese type 2 patients. Despite aggressive treatment, mortality rates remain high for both conditions, approaching 5% for DKA and 15% for the HHS. Mortality is associated with advanced age and comorbidity and is usually due to an associated catastrophic illness (e.g., myocardial infarction, cerebrovascular accident, sepsis) or to acute complications, including aspiration, cardiac arrhythmias, or cerebral edema. Treatment of hyperglycemic states therefore involves far more than the administration of insulin to reverse hyperglycemia; it also depends critically on the detection and treatment of precipitating illness, as well as prompt attention to fluid and electrolyte disturbances.

DIABETIC KETOACIDOSIS. DKA may herald the onset of type 1 diabetes but most often occurs in established diabetic patients as a result of an intercurrent illness (e.g., infection), an inappropriate reduction in insulin dosage, or missed insulin injections (especially in adolescents). A common scenario is a patient who fails to adjust insulin therapy and consume extra fluids during an illness. Other common precipitants of DKA (and the HHS) include myocardial infarction, cerebrovascular accident, and alcohol intoxication or abuse; a more extensive list of common precipitants appears in Table 242–9. Prevention of DKA requires extensive education in "sick day" insulin and fluid management as well as home-based assessment of urine ketones whenever severe hyperglycemia or physical illness is noted.

The three cardinal biochemical features of DKA—hyperglycemia, ketosis, and acidosis—result from the combined effects of deficient circulating insulin activity and the excessive secretion of counterregulatory hormones. These hormonal imbalances mobilize the delivery of substrates from muscle (amino acids, lactate, pyruvate) and adipose tissue (free fatty acids, glycerol) to the liver, where they are actively converted to glucose or to ketone bodies (β-hydroxybutyrate, acetoacetate, acetone); both are ultimately released into the circulation at rates that greatly exceed the capacity of tissues to use them. The end results are hyperglycemia (>250 mg/dL), ketoacidosis (pH <7.30), and an osmotic diuresis that promotes dehydration and electrolyte loss. Typically, the clinical history of DKA involves deterioration over days, with advancing polyuria, polydipsia, and other symptoms of worsening hyperglycemia; other common clinical features include weakness, lethargy, nausea, and anorexia. Abdominal pain in the setting of DKA is classically periumbilical and can mimic the acute abdomen. Reduced motility of the gastrointestinal tract or (in severe cases) paralytic ileus may further contribute to diagnostic confusion. Vomiting is an ominous symptom because it precludes oral replacement of fluid losses; severe volume depletion follows quickly. Physical findings in DKA are mainly secondary to dehydration and acidosis and include dry skin and mucous membranes, reduced jugular venous pressure, tachycardia, orthostatic hypotension, depressed mental function, and Kussmaul (deep, rapid) respirations. Ketosis is often recognizable by a sweet, sickly smell on the patient's breath.

The diagnosis of DKA is usually straightforward and should be made promptly. The clinical picture and the presence of hyperglycemia should alert the clinician to test for ketones and to measure arterial pH. Initial laboratory information to be gathered should include a complete blood cell count with differential, urinalysis, serum chemistries (a "Chem-10," including divalent cations), and cardiac enzymes; liver and pancreatic function tests should also be considered. An electrocardiogram and a chest radiograph should be performed, and cultures should be taken from blood, urine, and other potential sources as clinically indicated. In DKA, glucose levels vary from 250 to greater than 1000 mg/dL, serum bicarbonate drops below 18 mEq/L, and there is an excess anion gap that is generally proportional to the decrease in serum bicarbonate. Hyperchloremia may be superimposed if the patient maintains an adequate glomerular filtration rate (GFR) and is able to exchange ketoacid anions for chloride in the kidney. The degree of

Table 242–9 • PRECIPITANTS OF DIABETIC KETOACIDOSIS AND/OR THE HYPEROSMOLAR HYPERGLYCEMIC STATE

THE THREE MOST COMMON PRECIPITANTS
Infections (30–50%): pneumonia, urinary tract infections, sepsis, gastroenteritis, etc.
Inadequate insulin treatment (20–40%): includes noncompliance, insulin pump failure
Myocardial ischemia/infarction (3–6%): often clinically "silent" in diabetic patients
OTHER PRECIPITANTS
Cerebrovascular accident
Intracranial bleeding (e.g., subdural hematoma)
Acute pulmonary embolism
Intestinal/mesenteric thrombosis
Intestinal obstruction
Acute pancreatitis
Alcohol intoxication/abuse
Renal failure (± peritoneal dialysis)
Severe burns, hyperthermia, or hypothermia
Endocrine disorders: Cushing's syndrome, thyrotoxicosis, acromegaly
Total parenteral nutrition
Drugs:
Cardiovascular: beta-blockers, calcium channel blockers, diuretics, diazoxide, encainide
Immunosuppressant drugs, including corticosteroids
Miscellaneous: antipsychotics, phenytoin, cimetidine, pentamidine, L-asparaginase

depression of arterial pH depends largely on respiratory compensation. In mild cases, the pH may range from 7.25 to 7.30, while in severe cases it can fall below 7.00. In general, clinical severity of DKA depends more on the magnitude of acidosis than on hyperglycemia; as a result, arterial pH is widely used as a reference indicator of DKA severity. Occasionally, a degree of superimposed metabolic alkalosis (e.g., caused by vomiting or diuretic use) may obscure the true severity of ketoacidosis. An increased anion gap out of proportion to the fall of bicarbonate should suggest this possibility. Other laboratory abnormalities commonly seen in DKA include a reduced measured serum sodium level (due to hyperosmolarity and the resulting osmotic shift of water into the intravascular space), prerenal azotemia, and hyperamylasemia, which is usually of nonpancreatic origin and can lead to an erroneous diagnosis of pancreatitis. Normal, elevated, or reduced concentrations of potassium, phosphate, and magnesium may exist when DKA is diagnosed; however, large deficits of these electrolytes invariably accompany the osmotic diuresis and become readily apparent during the course of treatment.

Special care should be taken when interpreting serum or urine ketone results. Because quantitative measurements of β-hydroxybutyrate and acetoacetate are not readily available, rapid diagnosis usually requires *qualitative* assessment of serum ketones using serum dilutions and reagent strips (Ketostix) or tablets (Acetest), which depend on a nitroprusside reaction with acetoacetate. Acetone, however, reacts weakly with nitroprusside and β-hydroxybutyrate reacts not at all; as a result, qualitative testing for ketones can be misleadingly low. Furthermore, because of the presence of intracellular acidosis, β-hydroxybutyrate levels are often much higher than levels of acetoacetate, which may further conceal the true degree of ketoacidosis. Conversely, after insulin therapy begins, the nitroprusside reaction gives the "false" impression of sustained ketoacidosis for hours or even days, for two reasons: (1) β-hydroxybutyrate is converted to acetoacetate, creating an illusion of rising ketone levels, and (2) nonacidic acetone is cleared slowly from the peripheral circulation.

HYPEROSMOLAR HYPERGLYCEMIC STATE. The metabolic state formerly known as the hyperglycemic hyperosmolar nonketotic state/coma has been renamed the hyperosmolar hyperglycemic state (HHS), to highlight two important points: (1) ketosis (and acidosis) may be present to varying degrees in HHS, and (2) alterations in sensorium most commonly occur in the absence of coma. In fact, only 10% of HHS patients present with frank coma, and an equal percentage show no signs whatsoever of mental obtundation. The hallmarks of the HHS are severe hyperosmolarity (>320 mOsm/L) and hyperglycemia (>600 mg/dL). Severe hyperglycemia occurs because patients cannot drink enough liquid to keep pace with a vigorous osmotic diuresis; the resulting impairment in renal function further reduces glucose excretion through the kidney, leading to remarkable blood glucose elevations. In contrast to DKA, severe acidosis and ketosis are generally absent in the HHS; however, some type 2 patients with depressed endogenous insulin secretion may be unable to fully suppress ketone production in the face of elevated counter-regulatory hormones produced by physical illness. Because HHS patients have higher portal vein insulin concentrations than patients with DKA, ketoacid production by the liver is relatively mild, yielding only mild acidosis. In the HHS, in the absence of concurrent acid-base disturbances, arterial pH rarely drops below 7.30, and serum bicarbonate levels rarely fall below 18 mEq/L.

In the hyperosmolar hyperglycemic state, clinical severity and levels of consciousness generally correlate with the severity and duration of hyperosmolarity. Clinical signs indicate profound dehydration; gastrointestinal symptoms are less frequently seen than in diabetic ketoacidosis. A variety of often reversible neurologic abnormalities may exist, including grand mal or focal seizures, extensor plantar reflexes, aphasia, hemisensory or motor deficits, and/or worsening of a preexisting organic mental syndrome. The laboratory picture is dominated by the effects of uncontrolled diabetes and dehydration; renal function is impaired, hemoglobin is elevated, and liver function test results may be abnormal because of baseline hepatic steatosis. Although severe hyperglycemia would be expected to lower measured serum sodium, it is not uncommon to see "normal" or even "elevated" sodium levels because of the severity of dehydration. The serum osmolarity itself can be measured directly or can be estimated using the following formula, which excludes urea, since it is freely diffusible throughout the body and therefore has little influence on the osmotic pressure gradient:

$$\text{Effective osmolarity (mOsm/L)} = 2[\text{measured serum } Na^+ + K^+ \text{ (mEq/L)}] + [\text{glucose (mg/dL)}/18]$$

Rx Treatment

The initial goals of therapy for both hyperglycemic states are to replace fluid and electrolyte deficits and to slowly correct hyperglycemia. Unless severe, ketoacidosis will generally correct with these measures and requires no specific therapy. ADA management guidelines are presented in Figure 242–10 and summarized here. In the treatment of hyperglycemic states, special attention must be paid both to treatment of precipitating illness and to potential complications that may arise during (or as a result of) appropriate medical therapy.

In the early hours of treatment, the primary consideration is to restore intravascular volume, to correct tissue hypoperfusion and restore insulin sensitivity. With DKA, there can exist massive total-body deficits of water (5 to 10 L), sodium (5 to 10 mEq/kg), and other electrolytes (see later); losses are even more profound in the HHS. Although water loss usually exceeds the loss of sodium, it is almost always preferable to begin fluid replacement with isotonic normal saline (0.9% NaCl solution) for efficient volume restoration. Fluid replacement regimens vary, but it is common to administer 1 L of normal saline within the first hour, followed by continuous infusion with either 0.45% NaCl or 0.9% NaCl depending on the corrected serum sodium and the patient's hemodynamic status. Likewise, the rate of infusion (commonly 250 to 500 mL/hour) should be adjusted according to both biochemical responses and the clinical status of the patient (e.g., oliguria or underlying cardiovascular disease). In pediatric patients with DKA, isotonic solutions are generally preferred, since they are less likely than hypotonic solutions to accelerate water shifts into the intracellular space and contribute to cerebral edema. During the course of treatment, once blood glucose falls to below 250 or 300 mg/dL, glucose should be added to intravenous fluids to avoid eventual hypoglycemia and to minimize the risk of cerebral edema.

Although insulin resistance is present in both DKA and the HHS, supraphysiologic doses of insulin are unnecessary and are more likely to provoke hypokalemia, hypophosphatemia, and delayed hypoglycemia. A typical insulin replacement regimen uses an intravenous bolus of 0.15 U/kg of rapid-acting (e.g., regular) insulin, followed by 0.1 U/kg/hour thereafter. Smaller doses may be used in HHS. Intravenous administration is the most predictable way of delivering insulin to target tissues, particularly in severely hypovolemic patients with reduced peripheral blood flow. If intravenous administration is not possible, the intramuscular or subcutaneous routes of administration can be used. It is ideal if blood glucose levels fall at a steady and predictable rate (50 to 80 mg/dL/hour), so it is important to monitor blood glucose hourly during insulin therapy to ensure an appropriate rate of decline. Blood glucose should not fall too rapidly, especially in young children, in whom accelerated glucose correction has been associated with cerebral edema.

When reviewing the progress of treatment, it is important to consider a failure in insulin delivery if blood glucose fails to drop appropriately. In some patients, persistent hyperglycemia may be due to severe insulin resistance and necessitates an increase in the insulin dose. However, because the primary mechanism for lowering plasma glucose in the early stages of treatment is urinary glucose disposal (rather than insulin-stimulated glucose consumption), the problem may simply reflect inadequate replacement of intravascular volume, in which case insulin rates may not need to be increased. After a stable blood glucose level below 250 mg/dL has been achieved, subcutaneous administration of insulin can be started, and the intravenous insulin infusion may be discontinued. With DKA, it is best to overlap the intravenous and subcutaneous routes by 1 to 2 hours, to avoid the return of ketoacidosis. Following the return of normoglycemia, long-term medical management should be initi-

Continued

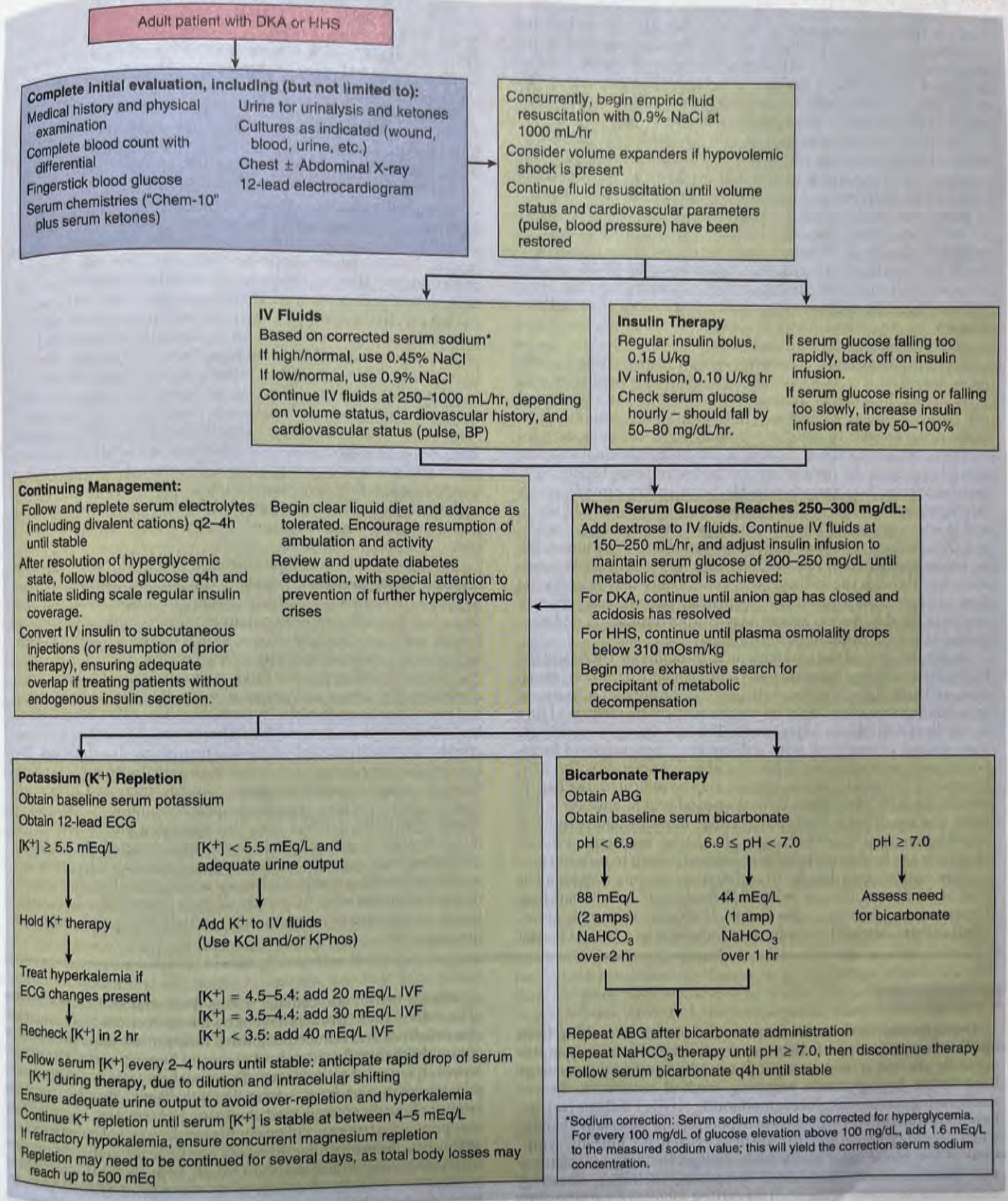

FIGURE 242–10 • Management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS).

ated (or resumed), and a standing order should be placed for the continuous delivery of "sliding scale" of subcutaneous short-acting insulin injections every 4 to 6 hours. The eventual dosage and frequency of insulin and/or oral agent therapy will depend on multiple factors, including body habitus, comorbidity, insulin sensitivity, and the effectiveness of prior therapeutic regimens.

Potassium replacement in DKA and the HHS is of vital importance. Hypokalemia can result in muscle weakness, cramps, and nausea, while both hyperkalemia and hypokalemia are associated with cardiac arrhythmia. At the time of initial evaluation, patients have a severe total-body potassium deficit (about 3 to 7 mEq/kg), yet measured serum potassium levels may be low, normal, or high, especially if acidosis or renal failure is present. Once intravenous fluids and insulin are started, serum potassium levels fall quickly because of an insulin-mediated shift of potassium into the intracellular space. In addition, fluid replacement causes extracellular dilution of potassium, leading to improved renal perfusion and increased urinary potassium excretion. This rapid decline can be countered by potassium replacement based on measured serum levels. A low potassium level (<3.5 mEq/kg) requires prompt treatment with up to 40 mEq/hr, whereas "normal" serum levels (3.5 to 5.5 mEq/kg) call for less aggressive repletion (10 to 30 mEq/hr), assuming adequate urine output. In patients who may have lost potassium for additional reasons, such as diuretic use or gastrointestinal loss, one should anticipate the need for greater potassium supplementation. Serial electrocardiograms are valuable, because they provide a more direct assessment of *intracellular* potassium; flat-to-inverted T waves and U waves suggest a low potassium level, while peaked T waves and QRS prolongation may indicate hyperkalemia. The intracellular potassium deficit in renal tubular cells further promotes potassium loss through the kidneys; this abnormality may take several days to correct. As a result, excess urinary potassium losses may continue for days to weeks and may call for prolonged oral supplementation to maintain normokalemia.

In the majority of patients with mild-to-moderate DKA (and the HHS), ketoacids clear spontaneously with standard therapeutic measures, and artificial correction with alkali (bicarbonate) is unnecessary. Suppression of lipolysis by insulin reduces free fatty acid flux to the liver and blocks ketogenesis. The remaining ketoacids are then cleared or oxidized, with subsequent regeneration of bicarbonate and restoration of pH. In cases of severe acidosis (pH < 7.0), however, bicarbonate administration may be indicated; the hyperventilatory drive of severe acidosis is uncomfortable, and severe acidosis also contributes to negative cardiac inotropy and peripheral vasodilation. Bicarbonate therapy should be used with caution because it can further provoke hypokalemia, which in turn can precipitate cardiac arrhythmias. In addition, by causing a sudden left shift of the dissociation curve for oxyhemoglobin, bicarbonate may impair oxygen delivery to the tissues. If alkaline therapy is given, small amounts should be administered, and slowly: 44 mEq (1 amp) of $NaHCO_3$ over 1 hour for a pH of 6.9 to 7.0, and 88 mEq over 2 hours for a pH of less than 6.9. Following bicarbonate administration, arterial pH (and serum potassium levels) should be rechecked every 2 hours, and alkaline therapy should be discontinued when the pH rises above 7.0.

In the setting of DKA, phosphate losses average 3 to 7 mmol/kg, whereas magnesium losses reach 1 to 2 mEq/kg; magnitudes of depletion for both ions may be greater for the HHS because of a more prolonged osmotic diuresis. Phosphate is shifted extracellularly during hyperosmolar states, so initial serum levels may be falsely elevated and may drop rapidly during therapy. Complications of hypophosphatemia generally occur at serum levels below 1.0 mg/dL and include respiratory and skeletal muscle weakness, impaired cardiac systolic performance, and hemolytic anemia. Phosphate depletion may also contribute to depressed concentrations of 2,3-diphosphoglycerate, thus shifting the oxygen dissociation curve to the left and limiting tissue oxygen delivery. Although prophylactic phosphate replacement has shown no clinical benefit in trials, phosphate repletion should be given to patients with serum phosphate levels below 1.0 mg/dL and to patients with evidence of cardiac or respiratory compromise, hypoxia, or hemolytic anemia. An effective means of replacing phosphate is to replace one third of potassium losses (discussed earlier) as potassium phosphate; in general, 20 to 30 mEq/L of potassium phosphate can be added to intravenous fluids and given over several hours. Because of calcium binding, hypocalcemic tetany may complicate phosphate therapy unless magnesium supplements are also provided; for this reason, serum calcium, phosphate, and magnesium levels should be monitored periodically during phosphate infusion.

The most common complications of therapy for hyperglycemic states are hypoglycemia, hypokalemia, hypophosphatemia, and fluid overload; precautions to avoid these complications have already been described. Two other rare but potentially fatal complications deserve special mention. Cerebral edema, which occurs primarily in pediatric patients, is associated with overaggressive correction of hyperglycemia and with hypotonic fluid replacement; it is likely the result of osmotically driven movement of water into the central nervous system when plasma osmolarity declines too rapidly. Clinically, cerebral edema is characterized by lethargy and headache, with progressive decline in mental status and neurologic deterioration. The acute respiratory distress syndrome is also attributed to rapid reductions in colloid osmotic pressure, causing increased lung water content, decreased lung compliance, and noncardiogenic pulmonary edema. Clinically, patients with this condition present with respiratory distress, hypoxemia with an elevated A-a gradient, and bilateral pulmonary congestion on the chest radiograph. In practice, a suspicion for either cerebral edema or acute respiratory distress syndrome requires prompt diagnosis; all such patients should be transferred to an intensive care unit for immediate and aggressive management.

HYPOGLYCEMIA

Hypoglycemia is the most frequent complication resulting from insulin therapy for type 1 diabetes; nearly all patients are symptomatically affected at least once per year, and a significant percentage have severe hypoglycemia requiring medical assistance. Recent studies using continuous glucose monitoring of type 1 diabetic patients have shown alarmingly high rates of hypoglycemia, especially at night, when sleeping patients are unaware of its existence. Clinically, symptoms of low blood sugar result from changes in autonomic activity and brain function. Autonomic symptoms, including sweating, tremor, and palpitations, are often the earliest subjective warning signs of hypoglycemia. Central nervous system symptoms and signs of glucose deficiency, termed neuroglycopenia, may be nonspecific (e.g., fatigue or weakness) or more clearly neurologic (e.g., double vision, oral paresthesias, slurring of speech, apraxia, or behavioral disturbances). Hypoglycemia affects type 2 patients as well; most cases occur during treatment with insulin or insulin secretagogues, especially the longer-acting sulfonylureas. Because of the long-acting nature of the oral agents, low blood sugar levels can recur up to 48 hours after drug withdrawal, and a more extended course of therapy is often required.

It is well known that prolonged, severe hypoglycemia can cause irreversible brain damage. What is less clear, however, is whether significant neurologic damage results from shorter, milder episodes of low blood sugar. Studies have shown that electroencephalographic abnormalities and reduced cognitive function are more prevalent in young children with a history of recurrent hypoglycemia. The DCCT, however, reported no evidence of neuropsychological impairment in patients with recurrent severe hypoglycemic episodes, after an average of 7 years of intensified treatment. Nevertheless, hypoglycemia may provoke seizures, accidental injury, and a catecholamine response, which can induce cardiac ischemia and/or arrhythmias in patients with underlying cardiac disease. Overall, hypoglycemia is thought to account for 3 to 4% of deaths in insulin-treated diabetic patients. Hypoglycemia also has far-reaching social implications: on a personal level, it can induce great fear, preclude comfortable engagement in routine activities (e.g., driving), and lead both patient and clinician to aim deliberately for less than optimal glycemic control. From a practical standpoint, the growing body of evidence that tight glucose control prevents long-term complications of diabetes has led to more aggressive treatment regimens, inevitably resulting in a greater incidence of clinical hypoglycemia. This, in turn, has necessitated further study of the physiology, consequences, and prevention of hypoglycemia in diabetic patients.

In *non*diabetic persons, hypoglycemia provokes a rapid, multitiered metabolic response intended to restore normal blood glucose levels. The brain cannot store more than a few minutes' supply of

energy; in the short term, its function is exclusively dependent on a constant supply of glucose for fuel. To preserve central nervous system function, spontaneous recovery from hypoglycemia involves both the activation of endogenous glucose production and reduced peripheral glucose utilization. Three fundamental mechanisms are responsible for this process: (1) the dissipation of endogenous insulin, (2) counter-regulatory hormone activity, and (3) the subjective awareness of hypoglycemia, resulting in hunger and subsequent carbohydrate ingestion. Early hormonal changes are triggered when plasma glucose approaches the hypoglycemic range (65 to 70 mg/dL). A rise in glucose production, attributable mainly to stimulation of hepatic glycogenolysis, is initiated by the release of glucagon from pancreatic α-cells in conjunction with falling levels of endogenous insulin. Catecholamines are also released, which produce "alarm" symptoms for hypoglycemia (e.g., hunger, tremor, palpitations) and further promote the synthesis of glucose, via stimulation of hepatic glycogenolysis, mobilization of substrates for gluconeogenesis, and further suppression of insulin production. When hypoglycemia is sustained, additional counter-regulatory hormones such as growth hormone and corticosteroids are released; through a variety of complimentary mechanisms, these hormones also help to promote continued glucose availability. Reduced peripheral glucose uptake results from an interplay of factors, including low circulating insulin levels, epinephrine's inhibitory effect on insulin-stimulated glucose uptake, elevated free fatty acid levels, and hypoglycemia per se. For a more in-depth discussion of metabolic responses to hypoglycemia, Chapter 243.

Type 1 diabetic patients are more prone to hypoglycemia for several reasons. First of all, injected insulin enters the circulation from a nonphysiologic source (e.g., a subcutaneous depot) and is therefore unaffected by counter-regulatory responses to falling glucose levels. In addition, type 1 patients lose their glucagon response to hypoglycemia, for unclear reasons; this appears to be a stimulus-specific phenomenon, since their glucagon response to other stimuli may be unaffected. Defective glucagon responses develop in most type 1 patients 2 to 5 years after diagnosis (usually at about the same time that they become severely insulin-deficient), after which time counter-regulation relies heavily on epinephrine release. Unfortunately, one-half of type 1 patients also undergo a stimulus-specific diminution in their epinephrine response to hypoglycemia, further predisposing them to severe hypoglycemia. Finally, the ability of type 1 diabetics to recognize hypoglycemia and take corrective action may also be impaired. In some cases, the irritability and confusion that occur during hypoglycemia may prevent the patient's awareness of its cause. In others, patients may lose the autonomic warning symptoms of hypoglycemia and may recognize (or fail to recognize) the condition only when somatic neurologic function becomes impaired. This so-called "hypoglycemic unawareness" syndrome has been associated with a number of factors, including a history of severe hypoglycemia, long duration of diabetes, and autonomic neuropathy.

Hypoglycemia unawareness commonly occurs when patients are switched to intensive insulin regimens. The introduction of intensified treatment regimens can lower the glucose threshold that triggers epinephrine release and adrenergic symptoms, which at least partly explains the increased frequency of severe hypoglycemia reported in the DCCT. The mechanism underlying the changes is an increased incidence of iatrogenic hypoglycemia during intensified insulin therapy. It has been shown that even brief periods of antecedent hypoglycemia can suppress counter-regulatory responses during subsequent hypoglycemic episodes; this effect persists for several days or weeks. On the bright side, defective glucose counter-regulation induced by intensive insulin regimens appears to be reversible, via scrupulous avoidance of hypoglycemia and readjustment of treatment goals; this underscores the need to prevent iatrogenic hypoglycemia by improving patients' self-management skills. Continuous glucose monitoring, by allowing more precise adjustments in the insulin regimen, can be expected to improve hypoglycemia unawareness and the diminished counter-regulatory response.

PATHOGENESIS OF CHRONIC DIABETIC COMPLICATIONS

The pathogenesis of the microvascular and neuropathic complications of diabetes is complex and poorly understood. Two well-researched mechanisms proposed for glucose-induced cell injury are advanced glycosylation end-products (AGEs) and an accelerated polyol pathway with consequent protein kinase C activation. These and other potential contributors are briefly discussed.

Proteins are readily glycosylated in vivo in direct proportion to prevailing levels of glucose. This nonenzymatic glycosylation is nonspecific, involving a wide range of proteins, including hemoglobin, collagen, laminin, low-density lipoproteins, and peripheral nerve proteins (tubulin). The consequent AGEs accumulate in a variety of tissues (including the kidneys and blood vessels) and are thought to contribute to cell injury through a variety of mechanisms, including stimulation of cytokines, complement activation, and upregulation of growth factor synthesis. AGEs also stimulate oxidative reactions, and their cross-linking capabilities render them resistant to natural degradation. In experimental diabetic animals, inhibition of AGE formation reduces tissue deposition of these end products and inhibits both the expansion of glomerular volume and urinary protein excretion.

In the polyol pathway, increased activity of intracellular aldose reductase leads to an accumulation of sorbitol and fructose, resulting in osmotic cell injury, decreased glutathione antioxidant activity (via decreased NAD+), and the enhanced formation of diacylglycerol. Diacylglycerol formation can in turn activate specific isoforms of protein kinase C, which stimulate transforming growth factor-β release and play an important role in cell proliferation and vascular permeability. Beneficial effects of both aldose reductase inhibitors and specific protein kinase C inhibitors have been consistently demonstrated in animal models of diabetes. To date, their value in human subjects is uncertain.

Other potential mechanisms through which glucose could impair cell function include (but are not limited to) (1) formation of reactive oxygen species (hydrogen peroxide, superoxide), (2) activation of cytokines (angiotensin II, endothelin), (3) growth factor stimulation (transforming growth factor-β, vascular endothelial growth factor), and (4) depletion of basement membrane glycosaminoglycans. Interventions directed at each of these mechanisms are currently under investigation.

Hemodynamic changes in the microcirculation may also contribute to microangiopathy. In the diabetic kidney, GFR is increased out of proportion to renal plasma flow, owing to an elevation in the transglomerular pressure gradient. It is assumed that raised glomerular pressures promote the passage of proteins and AGEs; with time, their accumulation in the mesangium could trigger the proliferation of mesangial cells and matrix production, eventually leading to glomerulosclerosis. Compensatory hyperfiltration would develop in less affected glomeruli, but even these would ultimately succumb because of progressive glomerular damage. Clinical studies support this view. Unilateral renal artery stenosis diminishes diabetic pathologic lesions in the affected kidney, and angiotensin converting enzyme (ACE) inhibitors (which reduce transglomerular pressure) are known to slow the progression of diabetic nephropathy. The diabetes-associated increase in microcirculatory hydrostatic pressure may also contribute to generalized capillary leakage of macromolecules in diabetic patients.

These theories would predict the benefits of optimal glycemic control reported by the DCCT in patients with mild or no complications. Whether similar benefits can be expected once severe damage has occurred is less clear. Extensive glycosylation of proteins with slow turnover rates would not be readily affected by correction of hyperglycemia. Moreover, the hemodynamic theory for nephropathy predicts that once glomerular injury causes compensatory hyperfiltration, progressive injury may continue in the remaining glomeruli, regardless of the prevailing metabolic state.

DIABETIC RETINOPATHY

Diabetic retinopathy refers to progressive pathologic alterations in the retinal microvasculature, leading to areas of retinal nonperfusion, increased vascular permeability, and the pathologic proliferation of retinal vessels. In the United States, diabetes is the leading cause of blindness in persons aged 20 to 74 years. Retinopathy in patients with poorly controlled type 1 diabetes occurs in about 25% of patients 5 years after diagnosis, in 60% at 10 years, and in more than 95% at 15 years. Blindness occurs 25 times more frequently in diabetic patients than in control subjects and is seen most often after the disease has been present for at least 15 years, in the setting of advanced retinopathy. Approximately 10 to 15% of type 1 diabetic patients will become legally blind (visual acuity of 20/200 or worse in the better eye). In type 2 diabetes, though the incidence of blindness is lower, higher disease prevalence results in an even larger number of patients affected with severe visual loss.

The earliest pathologic changes associated with retinopathy are termed *mild nonproliferative diabetic retinopathy* (*mild NPDR*). In type 1 patients, these changes generally begin 3 to 5 years after diagnosis. The first signs of mild NPDR are microaneurysms, which arise most often in areas of capillary occlusion. Subsequently, increasing vascular permeability leads to retinal blot hemorrhages (round, with blurred edges) and "hard" exudates (sharply defined and yellow). Infarctions of the nerve fiber layer, known as "soft" exudates or "cotton-wool spots," appear as white or gray, rounded swellings. At this early stage of retinopathy, visual acuity is generally unaffected, and the risk of progression to high-risk proliferative diabetic retinopathy (PDR) (see later) is about 15% at 5 years. *Moderate NPDR* is characterized by intraretinal microvascular abnormalities, including venous caliber changes, beading, and increased capillary dilatation and permeability. Later changes, termed *severe* or *very severe NPDR*, include progressive retinal capillary loss and ischemia, with further development of extensive hemorrhages, exudates, and microaneurysms. At 5 years, moderate and severe NPDR are associated with a 30% and 60% risk of progression to high-risk PDR, respectively.

Proliferative diabetic retinopathy involves neovascularization, the growth of fine tufts of new blood vessels and fibrous tissue from the inner retinal surface or the optic head. Early proliferative changes are confined to the retina, but later invasion of the vitreous body constitutes *high-risk PDR*; during this end stage, fibrosis and contracture of the neovasculature results in retinal detachment and hemorrhage, the most important determinants of blindness. Occasionally, new vessels can invade the iris and anterior chamber, leading to sight-threatening closed-angle glaucoma.

Clinically significant macular edema (CSME) results from vascular leakage at the macula and can occur either with or without the stages of retinopathy described earlier. CSME is suggested by hard macular exudates on fundoscopic examination and can be confirmed with slit lamp biomicroscopy. In general, maculopathy is more common in type 2 patients, in whom it is an important contributor to the loss of visual acuity. As will be discussed, the treatment of CSME runs parallel to the treatment of other forms of diabetic retinopathy.

Rx Treatment

At present, medical management of diabetic retinopathy is aimed at controlling risk factors for progression. The value of tight glycemic control was proven by the DCCT, whose primary prevention arm demonstrated an impressive 76% risk reduction for the onset of retinopathy with intensive therapy. In the secondary prevention arm, patients with early NPDR undergoing intensive therapy demonstrated a 47% risk reduction in the development of severe NPDR or PDR, a 51% risk reduction in the need for laser treatment, and a 26% risk reduction in the development of CSME. Other targets for medical management, all associated with accelerated retinal damage, include (1) hypertension, (2) hyperlipidemia, (3) treatment of nephropathy, and (4) careful follow-up during pregnancy, where accelerated retinal pathology has been linked to preexisting diabetes (but not gestational disease).

Surgical management of retinopathy is aimed at slowing disease progression, as baseline visual acuity is difficult to recover. In the 1980s, large-scale prospective clinical trials such as the Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study established photocoagulation as the treatment of choice when retinopathy threatens vision. Most patients with PDR, and selected patients with severe NPDR, are now treated primarily with scatter (panretinal) photocoagulation; cryotherapy or vitrectomy may be required if laser treatment is unfeasible for technical reasons or because of extensive disease. CSME is near-universally treated with focal photocoagulation, with the possible exception of patients exhibiting no or minimal NPDR. In such patients, close follow-up at 2- to 4-month intervals is an acceptable option. A treatment chart, adapted from a thorough technical review by Aiello et al, is shown in Table 242–10. Note that the decision to treat depends not only on stage of retinopathy and extent of CSME but also on general medical status, compliance with follow-up, and status of the contralateral eye.

These considerations make it imperative for physicians to prospectively identify diabetic patients at risk for retinopathy and visual loss. Nonspecialists, including house officers, internists, and diabetologists, are known to have difficulty diagnosing the stages of retinopathy; studies show that such physicians arrive at the correct diagnosis in fewer than half of cases. Accordingly, patients should be referred to an experienced ophthalmologist for a complete examination, to include a dilated fundoscopic examination, tonometry, and slit lamp biomicroscopy. The most recent ADA position statement recommends initial eye examination within 3 to 5 years of diagnosis of type 1 diabetes, and at the time of diagnosis in type 2 patients. Two special circumstances deserve a footnote here: (1) since children rarely develop retinopathy before puberty, early-onset type 1 patients generally do not require screening before 10 years of age, and (2) the acceleration of retinopathy during pregnancy demands that all patients with preexisting diabetes be examined during the first trimester. Follow-up of all patients should occur at least on a yearly basis, with the possible exception of retinopathy-free type 2 diabetics. Even in the latter cases, the ADA does recommend yearly examinations to avoid lost follow-up and to identify patients with more aggressive ocular disease.

DIABETIC NEPHROPATHY

End-stage renal disease (ESRD) from diabetic nephropathy (Chapter 118) is a major cause of morbidity and mortality, particularly in patients with type 1 diabetes, affecting 30 to 35% of patients in the United States. Although nephropathy is about one half as frequent in type 2 diabetics (partially due to a shortened life expectancy), type 2 diabetes still makes up the vast majority of diabetic patients seeking therapy for ESRD. Overall, diabetes is the leading cause of ESRD in the United States, accounting for more than one third of cases.

Details are less clear in patients with type 2 diabetes, but the natural history of diabetic nephropathy in type 1 diabetes is well described (Fig. 242–11). The period immediately following diagnosis is best characterized by glomerular hyperfiltration. During this time, there is renal hypertrophy, increased renal blood flow, increased glomeru-

Table 242–10 • GUIDELINES FOR TREATMENT AND FOLLOW-UP OF DIABETIC RETINOPATHY

STAGE OF RETINOPATHY	PANRETINAL PC	IF CSME, FOCAL PC*	FOLLOW-UP
No to minimal NPDR	*Not* recommended	Possible	12 months†
Mild to moderate NPDR	*Not* recommended	Probable	6–12 months†
Severe to very severe NPDR	Possible	Recommended	2–4 months
Early PDR	Probable	Recommended	2–4 months
High-risk PDR	Recommended	Recommended	2–4 months

*If retinopathy and CSME coexist, focal PC for CSME should always precede panretinal PC.
†In these patients, follow-up is recommended in just 2–4 months if CSME is also present.
CSME = clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PC = photocoagulation; PDR = proliferative diabetic retinopathy.
Adapted from Aiello LP, et al: Diabetic retinopathy (Technical Review). Diabetes Care 1998;21:143–156.

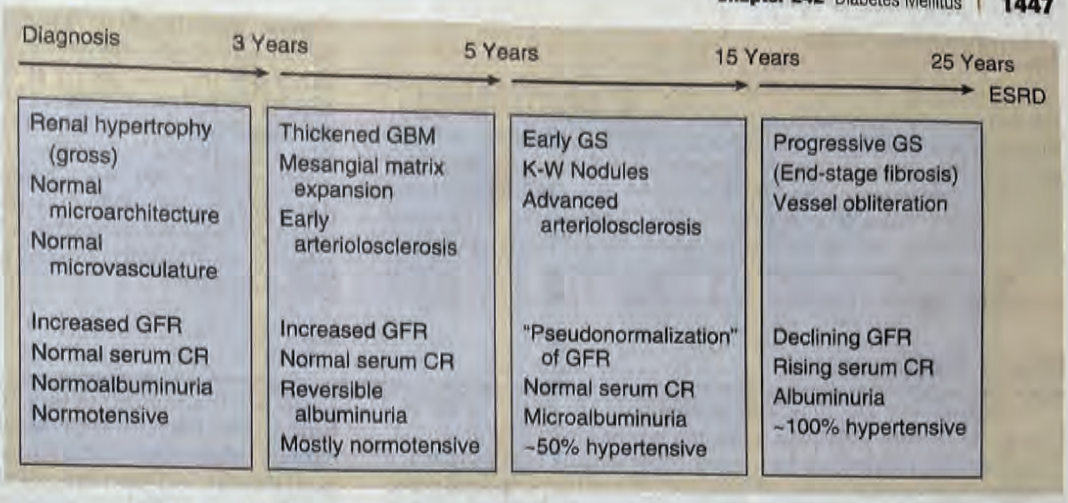

FIGURE 242–11 • The natural history of diabetic nephropathy in type 1 diabetic patients. Left untreated, end-stage renal disease (ESRD) develops in most patients within 10 years after a rise in serum creatinine (reflecting an approximately 50% decline in GFR). Fortunately, early intervention with glycemic control, angiotensin converting enzyme inhibitions, and antihypertensive therapy can slow the progression of disease. CR = creatinine; GBM = glomerular basement membrane; GFR = glomerular filtration rate; GS = glomerulosclerosis.

lar volume, and an increased transglomerular pressure gradient, all contributing to a rise in GFR. Importantly, these changes depend at least in part on hyperglycemia, as they are diminished by intensive diabetes treatment. Three to 5 years after diagnosis, early glomerular lesions appear, characterized by thickening of glomerular basement membranes, mesangial matrix expansion, and arteriolosclerosis. Albumin excretion remains low during early glomerular changes; however, as pathologic changes mount, the glomeruli lose their functional integrity, resulting in glomerular filtration defects and increased glomerular permeability. Although results of routine tests of renal function (creatinine and urinalysis) still remain normal, microalbuminuria (30 to 300 mg/day) appears. Systemic hypertension is also present at this time in more than 50% of cases.

After several years, most diabetic patients exhibit diffuse glomerulosclerosis, although a minority have pathognomonic Kimmelsteil-Wilson nodular lesions. Although pathologic changes continue to mount throughout the disease, glomerulosclerosis extensive enough to cause ESRD develops in a minority of patients; in these cases, overt albuminuria (>300 mg/day) begins approximately 15 years after diagnosis. Soon after, following a variable period on the order of 3 to 5 years, the GFR begins a relentless decline (≥10 mL/min/year), which is eventually reflected by an increase in serum creatinine. The appearance of massive proteinuria and the nephrotic syndrome is common in this context and often heralds progression to ESRD. Once the serum creatinine rises (reflecting an approximately 50% decline in GFR), ESRD develops in most patients within 10 years. This course is highly variable, however, particularly in type 2 diabetics, who may exhibit moderate proteinuria for several years without a substantial deterioration of renal function. A simple but useful method of monitoring progression to renal failure is to plot the reciprocal of the serum creatinine as a function of time. This technique allows better assessment of both therapeutic interventions and the time when renal replacement therapy will become necessary.

There are several known risk factors for the development of diabetic nephropathy, including duration of disease, elevated glycohemoglobin levels, and the presence of concurrent hypertension, hyperlipidemia, and tobacco use. Race is known to play a major role as well, as demonstrated by a higher prevalence of nephropathy in African American, Hispanic, and Native American patients. There is also a high concordance rate in families, with studies in both type 1 and type 2 diabetic families revealing a three- to four-fold increase in the prevalence of nephropathy with affected siblings.

Rx Treatment

Treatment of nephropathy has become an important focus of recent research and depends heavily on stage of disease. Early in the course of diabetes (before the onset of microalbuminuria), strict glycemic control is of the utmost importance. The DCCT demonstrated that intensive therapy reduced microalbuminuria by 39% and overt albuminuria by 54% in type 1 diabetic patients. A similar result was demonstrated in the UKPDS of type 2 diabetic patients, in which a less dramatic improvement in glycemic control reduced microalbuminuria and overt albuminuria by 24% and 33%, respectively. In normotensive type 2 diabetic patients, treatment with ACE inhibitors retards microalbumin production, and blood pressure lowering appears to be responsible for only part of this effect. Randomized trials using ACE inhibitors and angiotensin II receptor blockers have consistently shown a delay in the progression of both proteinuria and declining GFR,[7–9] and these classes of drugs have become the first choice for lowering blood pressure to 120 mm Hg or lower in diabetic patients (Chapter 63).

Once clinical nephropathy becomes evident, aggressive efforts at strict glycemic control have marginal value in slowing the progression of nephropathy. As described earlier, efforts aimed at reducing hypertension and glomerular pressure become the mainstay of therapy. Dietary protein restriction (i.e., 0.8 g/kg of body weight) may add limited benefit, and aggressive lipid management is useful in preventing both renal and extrarenal vascular complications. As ESRD approaches, long-term treatment plans should proceed much as they would in nondiabetic uremic patients, but therapy should be initiated sooner. It is well known that diabetic patients have a poorer tolerance for uremia than their nondiabetic counterparts; protein wasting is accelerated, hypertension becomes more difficult to control, and there is acceleration of generalized atherosclerosis with extensive cardiovascular morbidity. Current options for ESRD patients include hemodialysis, peritoneal dialysis, kidney transplantation, and a combined kidney-pancreas transplantation. Decisions among these options are complex (and beyond the scope of this chapter) and must be made on an individual basis. Finally, it should be noted that mortality associated with both dialysis and organ transplantation is higher in diabetic than nondiabetic patients, usually because of cardiovascular comorbidity and the more rapid development of complications such as vascular insufficiency.

It should be briefly noted here that glomerular nephropathy is not the only entity that commonly affects the genitourinary system in diabetic patients. Asymptomatic bacteriuria and pyelonephritis are twice as common in diabetic women, owing to several factors, including autonomic bladder dysfunction, impaired organ perfusion, and glycosuria. Papillary necrosis is associated with diabetes in more than one half of cases, and renal artery stenosis is more common as well. Hyperkalemia is another frequent complication of diabetes, due to a variety of factors including insulin deficiency, metabolic acidosis, reduced GFR, use of ACE inhibitors, and the syndrome of hyporeninemic hypoaldosteronism commonly seen in elderly patients with impaired renal function. Finally, diabetic patients are at notable risk for azotemic complications following the injection of contrast dye for radiologic studies. For this reason, aggressive pre- and post-radiology hydration with intravenous fluids is critical in these cases.

DIABETIC NEUROPATHY

Symptomatic, potentially disabling neuropathy affects nearly 50% of diabetic patients. It is usually symmetric but can be focal and frequently involves the autonomic nervous system as well. The prevalence of symmetric neuropathy is similar in type 1 and type 2 diabetes, whereas focal syndromes are more common in older, type 2 patients. Diabetes is the most common cause of neuropathy in developed nations of the world and is the leading cause of nonhealing skin ulcers and limb amputation.

The term *diabetic neuropathy* describes a wide variety of clinical syndromes, representing a complex interplay of pathogenic factors. Chronic, more insidious neuropathies may be mediated by metabolic factors, whereas the more acute, self-limiting neuropathies most likely have a vascular cause. Nerve growth factor is diminished in the nerves of patients with neuropathy, perhaps limiting regenerative capacity. Autoimmune mechanisms may also be involved: in affected type 1 diabetics, autonomic nerve bundles may show monocytic infiltration, and their sera may contain complement-fixing antibodies to sympathetic ganglia. Because of the multifactorial nature of diabetic neuropathy, current classification schemes are based largely on clinical presentation. Current taxonomy includes focal, diffuse, and autonomic neuropathies.

Clinical Manifestations

Patients with focal diabetic neuropathies (mononeuropathies) typically present with pain, although motor losses and abnormal deep tendon reflexes can be present. They usually begin suddenly, suggesting a vascular cause. Although any cranial or peripheral nerve can be involved, the most common sites include the oculomotor, median, radial, and lateral popliteal nerves. Painful radiculopathy may also occur in the distribution of one or more spinal roots and can easily be confused clinically with internal organ disease or postherpetic neuralgia. Because of the self-limited nature of focal neuropathy, treatment is generally aimed at pain control, with physical therapy as needed to maintain function of affected muscle groups. Focal neuropathies are generally self-limited, with an average duration of 6 to 8 weeks; chronicity can occur but is less common. Entrapment syndromes are more common in diabetic patients and may be distinguished by their more gradual onset, slow progression, and persistence with time. Entrapment sites include the median (carpal tunnel syndrome), ulnar, and radial nerves; lower extremity nerves such as the lateral popliteal, peroneal, and plantar nerves can also be involved. Conservative treatment of entrapment syndromes involves splinting and the use of anti-inflammatory medication. Surgical correction can be curative.

Distal symmetric (sensorimotor) polyneuropathy is the most common neurologic syndrome seen in diabetes. This process involves all somatic nerves but has a strong predilection for distal sensorimotor nerves of the feet and hands. Sensory fibers are generally preferentially affected; disease affects both small, unmyelinated C fibers (transmitting pain and temperature) and larger, myelinated Aδ/Aβ fibers, which carry touch, vibration, and proprioception. Early on, most patients with distal neuropathy are asymptomatic, with subtle abnormalities on examination, including the loss of vibration sense, light touch, two-point discrimination, and thermal sensitivity. Once symptomatic, patients typically report numbness and tingling of the distal extremities, often in the classic "stocking-glove" distribution. Pain is also common and can be C-fiber pain (burning, dysesthesia, and allodynia) or the large-fiber variety, usually described as "gnawing" or like a toothache. Severe, spontaneous, short-lived lancinating pains may also occur. Left unchecked, all types of pain may gradually gain in intensity, with a tendency to worsen at night, and there may be progressive loss of sensorimotor function as well. Later stages of disease can involve severe sensory loss, small muscle wasting of the hands and feet, sensory ataxia, and neuropathic arthropathy (Charcot joints). Foot ulceration can occur anywhere in the course of disease but is more common in advanced stages. Treatment, as will be discussed, is generally aimed at pain control and the slowing of symptom progression. Acute sensory neuropathy, a rapid-onset variant of symmetric polyneuropathy, usually occurs in the setting of altered metabolic control (e.g., DKA) or during initiation of insulin therapy ("insulin neuritis"). In this condition, C-fiber symptoms predominate. Acute sensory neuropathy carries a better prognosis than its chronic counterpart, with many patients achieving complete resolution.

Proximal motor neuropathy (diabetic amyotrophy), although classified as a polyneuropathy, is a unique condition that deserves special mention. This syndrome primarily affects elderly type 2 patients and is more common in men. It classically begins with pain in the thighs, hips, and buttocks, followed by weakness and atrophy of the proximal pelvic muscle groups. Iliopsoas, obturator, and adductor muscles of the pelvis are preferentially affected, with relative preservation of the hamstrings and gluteal muscles. In advanced cases, patients exhibit the inability to rise from a seated position (Gower's maneuver). Proximal motor neuropathy can be secondary to a number of other diseases, all more common in diabetic patients but not directly related to hyperglycemia. These include chronic inflammatory demyelinating polyneuropathy, monoclonal gammopathy, and vasculitis, all of which should be ruled out before the diagnosis of diabetic amyotrophy is made. This form of neuropathy has a good prognosis, with most cases resolving spontaneously in 12 to 24 months. Therapy is primarily supportive.

Symptomatic autonomic diabetic neuropathy carries a poor prognosis. Autonomic neuropathy typically accompanies other chronic complications of diabetes and may play a pathogenetic role through disturbed regulation of local blood flow. The manifestations of autonomic neuropathy are protean. Common syndromes are discussed here, grouped by organ system.

CARDIAC. Common cardiovascular abnormalities seen with autonomic neuropathy include resting tachycardia, diminished heart rate variability, and prolonged QTc. Diabetic patients often have defective heart rate and blood pressure responses to exercise, and their lack of autonomic regulation places them at high risk for silent myocardial ischemia, congestive heart failure, and sudden cardiac death. Unfortunately, no specific treatments are available for these conditions. Recent efforts to identify patients at risk for cardiac complications allow only for closer follow-up and appropriate treatment of coexisting cardiovascular risk factors.

VASCULAR. Postural hypotension is likely caused by an impaired sympathetic vasoconstrictor response and impaired cardiac reflexes. Non-neurogenic causes of orthostasis, such as volume depletion, impaired cardiac function, and infectious causes should be ruled out before the diagnosis is made. Tilt table testing can be useful to confirm the diagnosis. Nonpharmacologic measures, such as a raised-head position at night, reduction of rapid positional changes, and supportive elastic garments can be useful in mild cases. Disabling disease may require pharmacologic intervention; first-line agents include mineralocorticoids (9-α-fluorohydrocortisone), α-agonists (midodrine), and β-blockers with intrinsic sympathomimetic activity (pindolol). Clonidine, ergotamine-caffeine combinations, yohimbine, octreotide, and desmopressin can also be useful in selected cases. Often, the side effects of these agents limit their use; one must exercise caution before prescribing any of these agents to patients with diabetes.

GASTROINTESTINAL. Altered gastrointestinal function is commonly seen in patients with diabetes. Constipation is the most common clinical syndrome. Diarrhea is another frequent complaint and can be caused by a variety of conditions, including hypermotility (impaired sympathetic inhibition), hypomotility with bacterial overgrowth, pancreatic insufficiency, and bile salt irritation. Treatment is generally aimed at the underlying condition and may include antidiarrheals, broad-spectrum antibiotics, pancreatic enzymes, and bile acid sequestrants (cholestyramine). Gastroparesis is a particularly disabling condition, often manifesting with bloating, early satiety, nausea, and vomiting. Treatment of gastroparesis begins with small, frequent meals and the use of metoclopramide, a central dopaminergic agonist with gastric cholinergic activity. Early treatment is useful, but the drug's effect may diminish over time. Erythromycin, which acts on the motilin receptor to promote gastric motility, can also be considered.

GENITOURINARY. Impaired parasympathetic innervation leads to bladder hypotonia, incomplete bladder emptying, dribbling, and overflow incontinence. Bethanecol, a parasympathomimetic agent, can be helpful in reversing these symptoms, but its use is often limited by side effects including salivation, lacrimation, diarrhea, and bronchoconstriction. α-Blockers help by relaxing the urinary sphincter.

but these agents can potentiate postural hypotension, already prevalent in diabetic patients. Advanced cases of bladder dysfunction often require intermittent catheterization or the placement of an indwelling catheter. Erectile dysfunction is commonly seen in male diabetic patients. Injections of locally acting vasomotor agents, such as alprostadil and papaverine, have been used with moderate success but carry the risk of priapism, infection, and local fibrosis with repeated use. Sildenafil, a selective inhibitor of phosphodiesterase type 5, inhibits local breakdown of cyclic guanosine monophosphate, which in the presence of nitric oxide leads to selective engorgement of the corpus callosum. Sildenafil has demonstrated efficacy in the context of diabetes, but caution should be used in patients with suspected coronary disease, and the drug is contraindicated in combination with nitrate therapy. In refractory cases, referral to a urologist for a penile prosthetic implant should be considered.

SUDOMOTOR DYSFUNCTION. Abnormal sweat production in diabetic patients can result in xerosis and cracking of the skin, further predisposing these patients to cutaneous infections. Distal anhydrosis with compensatory truncal-facial sweating may occur, whereas generalized anhydrosis can produce heat intolerance and increase the risk of hyperthermia and heat stroke. An impaired sweat response can also further impair the diabetic patient's ability to recognize hypoglycemia. Current therapy for sudomotor dysfunction is limited to behavioral modification (i.e., heat avoidance), topical moisturizers, and intensive skin care. Local sympathectomy for hyperhydrosis should be considered only in severe, refractory cases.

Diagnosis

Diagnosing diabetic neuropathy can be a difficult task. It begins with a careful history and detailed neurologic examination, including detailed sensory testing (Semmes-Weinstein monofilament, two-point discrimination, 128 cps tuning fork, thermal discrimination), motor/gait examination, and documentation of deep tendon reflexes. Electrophysiologic studies, such as nerve conduction velocity studies and electromyography, are of use in firming up the diagnosis, although it should be noted that unmyelinated C-fiber neuropathy is undetectable with these methods. Nerve biopsy can occasionally be helpful to rule out other causes of neuropathy but is generally not recommended for diagnosis. If diffuse neuropathic symptoms are predominantly sensory in nature, work-up for additional causes of neuropathy should include testing for human immunodeficiency virus, vitamin B_{12} levels, SPEP/SIEP (serum protein electrophoresis/serum immunoelectrophoresis), and additional testing where indicated in suspected cases of porphyria, heavy metal intoxication, and paraneoplastic syndromes.

Rx Treatment

Early treatment of diabetic neuropathy should include tight glycemic control. In the DCCT, intensive therapy slowed the onset of neuropathy by 70% and slowed the progression of early neuropathy by 57%, while in the UKPDS, glucose control was associated with improved vibratory sensation. The potential use of recombinant nerve growth factor treatment has been quelled for the moment, after large multicenter trials failed to demonstrate clinical efficacy. Other potential treatments still in the investigational stage include aldose reductase inhibitors, ACE inhibitors, the antioxidant α-lipoic acid, and γ-lineoleic acid, an important constituent of neuronal membrane phospholipids.

There are several therapies for neuropathic pain whose use has been supported by randomized controlled trials. Tricyclic antidepressants, including amitriptyline, desipramine, and nortriptyline, are moderately effective and well tolerated at low doses, but dose escalation can result in drowsiness, anticholinergic effects, potentiation of cardiac arrhythmias, and worsening of glaucoma. Anticonvulsants, such as carbamazepine and gabapentin, may also be effective, although the former can cause hematologic abnormalities, whereas patients taking the latter may report dizziness, fatigue, headaches, or diarrhea. Topical therapies, such as capsaicin (which depletes stores of axonal substance P), clonidine, and lidocaine can be moderately effective. Additional oral agents to be considered include mexiletine, an oral lidocaine analogue, and tramadol, a centrally acting reuptake inhibitor with opiate activity. In refractory cases, long-term opiate use and consultation with a specifically trained pain specialist may be required.

DIABETIC FOOT

The diabetic foot is characterized by slowly healing plantar ulcers that result from apparently insignificant trauma. Left untreated, superficial ulcers may penetrate to underlying tissues, leading to complications including cellulitis, abscess formation, joint sepsis, and osteomyelitis. Gangrene may occur, and in severe cases amputation may be required. Overall, about 15% of diabetic patients experience clinically significant foot ulceration. Risk factors for ulcer development include long-standing diabetes, poor glycemic control, and concurrent diabetic complications; visual loss may also contribute to difficulties with self-care. Affected diabetic patients may eventually require amputation, with diabetes accounting for more than one half of nontraumatic lower extremity amputations in the United States. In the United States, the total costs of caring for diabetic foot ulcers are estimated at more than 6 billion dollars annually.

To varying degrees, the diabetic foot is characterized by chronic sensorimotor neuropathy, vascular disease, autonomic neuropathy, and impaired immune function. Sensory neuropathy prevents the detection of minor traumatic events, so that ill-fitting shoes (or sharp objects in the shoe) may erode the skin surface without signaling pain. Pedal neuropathy also produces abnormalities in both proprioception and intrinsic muscle motor function, pathologically altering weight distribution on the metatarsal heads and leading to "clawing" of the metatarsophalangeal joints. In advanced cases, abnormal loading of the foot can result in repeated painless fractures and the displacement of normal joint surfaces, producing so-called Charcot joints. Aortic and peripheral vascular disease often coexist. Diminished cardiac output and/or disturbed autoregulatory mechanisms of the microcirculation may further contribute to impaired blood flow and delay ulcer healing. Finally, abnormal immune function (secondary to severe hyperglycemia) can predispose to infection, further slowing wound closure and increasing the likelihood of ulcer complications.

Prevention of the diabetic foot parallels general diabetic care, with emphasis on proper nutrition, tight glycemic control, and medical risk factor modification, including smoking cessation. A general foot care prescription (Table 242–11) is valuable, and office visits should routinely include careful examination of the feet. In affected patients, a specialist examination is recommended at least once per year. In cases of deformed feet, pressure relief (off-loading) is essential and may include the use of orthotics, specialty shoes, assistive devices, and a total contact cast to direct pressure away from a high-risk area. Once an ulcer has formed, it should be treated aggressively with antibiotics, appropriate local wound care, and débridement of necrotic tissue. In selected cases, newer FDA-approved treatments should also be considered. Local application of recombinant human platelet-derived growth factor can moderately accelerate wound healing. Bioengineered tissue therapies, containing human dermal-epidermal components,

Table 242–11 • FOOT CARE PRESCRIPTION FOR DIABETIC PATIENTS WITH LOWER EXTREMITY SENSORY NEUROPATHY

Never walk barefooted
Do not apply hot water or heating pads to the feet
Inspect the feet daily, using a mirror for plantar surfaces
Wash the feet daily, drying thoroughly between the toes
Lubricate dry skin to avoid cracking
Wear properly fitting, well-cushioned shoes (insoles)
Break in new shoes slowly
Consider a second pair of shoes at night (larger size for dependent edema)
Cut toenails straight across, to conservative lengths
Schedule regular visits to a diabetic footcare specialist

have also shown some efficacy in early clinical trials; these products act as biologic dressings and contain live human fibroblasts, which deliver growth factors and extracellular matrix components directly to damaged skin. For extensive cases of gangrene or deep tissue infections, surgical amputation may be required. A compromised peripheral circulation makes such an outcome more likely. If poor circulation is present, a vascular surgeon should be consulted for consideration of angioplasty or vascular bypass.

HYPERTENSION, DYSLIPIDEMIA, AND CARDIOVASCULAR DISEASE

Atherosclerosis involving the coronary, cerebral, and peripheral (lower extremity) arteries is the predominant cause of diabetes-related mortality. The atherosclerotic process in diabetes is indistinguishable from that of the nondiabetic population but begins earlier and is often more severe. A predilection to cardiovascular disease is observed over the entire spectrum of diabetes, from poorly controlled insulin-dependent patients to those with mild, diet-controlled hyperglycemia or IGT. For unclear reasons, the disparity between diabetic and nondiabetic subjects is more pronounced in women. When accompanied by other major cardiovascular risk factors such as hypertension, dyslipidemia, and smoking, diabetes markedly increases the incidence of macrovascular complications. For example, the observed two- to three-fold greater risk of myocardial infarction with diabetes rises to eight-fold in the presence of hypertension, and to nearly 20-fold if both hypertension and dyslipidemia are present; smoking raises these risks even further. As a result, the diagnosis of diabetes mellitus should quickly prompt both an exhaustive search for coexisting cardiovascular risk factors and the initiation of aggressive preventive measures. This view is supported by recent data demonstrating that intensive intervention that targets multiple risk factors decreases the risk of cardiovascular events in patients with type 2 diabetes.

Diabetes is an independent risk factor for accelerated atherosclerosis. Its association with vascular disease is not solely attributable to an increased prevalence of other recognized vascular risk factors such as hypertension, smoking, and dyslipidemia. Many abnormalities induced by the diabetic state may contribute to atherosclerosis, including lipid abnormalities (e.g., increased total very low density lipoprotein, increased small dense [atherogenic] low-density lipoprotein, decreased high-density lipoprotein, increased lipoprotein oxidation, increased lipoprotein glycosylation, decreased lipoprotein lipase activity), accentuated platelet aggregation and adhesion, endothelial cell dysfunction, and an induced procoagulant state (e.g., increased clotting factors and fibrinogen, decreased levels of antithrombin III, protein C, and protein S, and decreased fibrinolytic activity). These changes are thought to be in large part due to the presence of insulin resistance. It has been suggested that hyperinsulinemia per se might also contribute to macrovascular disease; proposed pathogenetic mechanisms include insulin-induced stimulation of vascular endothelial and smooth muscle cells, enhanced insulin-like growth factor 1 expression, and the augmented synthesis of atherogenic factors such as endothelin and plasminogen activator inhibitor.

In patients with diabetes, systemic hypertension is an important cofactor in the development of cardiovascular disease, nephropathy, and retinopathy (Chapter 63). In type 2 patients, the prevalence of hypertension is more than twice that of the nondiabetic population, largely due to the clustering of both disorders in patients with obesity and insulin resistance. Type 1 patients, in contrast, are usually normotensive in the absence of renal disease; if nephropathy develops, the majority of affected patients will then develop secondary hypertension. The importance of aggressive blood pressure management in diabetes has been established by the UKPDS (see earlier): in the study, blood pressure reduction (with ACE inhibitors or β-blockers) in type 2 diabetic patients with hypertension produced striking decreases in both cardiovascular and microvascular outcomes. Subsequent prospective trials, including the Systolic Hypertension in the Elderly Program (SHEP), the Systolic Hypertension in Europe (Sys-Eur) Trial, and the Hypertension Optimal Treatment (HOT) trial, have confirmed the value of aggressive blood pressure goals in reducing major cardiovascular events in diabetic patients. Based on these and other studies, the Joint National Committee VI (JNC VI) has established blood pressure targets of less than 130/85 for patients with diabetes mellitus; even stricter reductions (<125/75) are recommended in the presence of established nephropathy.

Rx Treatment

The choice of antihypertensive agent for diabetic patients has for years been the subject of considerable research and debate. Among the various therapeutic options, ACE inhibitors and angiotensin II receptor blockers may offer special advantages, as they have consistently demonstrated the ability to lower intraglomerular pressures and to slow the progression of albuminuria and diabetic nephropathy. JNC VI has endorsed α-adrenergic antagonists, calcium channel antagonists, and low-dose diuretics as the preferred alternative agents for use in diabetic patients, due to neutral or favorable effects on insulin sensitivity and glucose control. β-Blockers should also be strongly considered, particularly in the setting of concurrent cardiovascular disease, including prior myocardial infarction, mild-to-moderate congestive heart failure, and cardiac arrhythmias. Prospective trials comparing antihypertensive agents in diabetic patients have yielded mixed results. In the UKPDS, β-blockers were as effective as ACE inhibitors in reducing adverse cardiac and microvascular outcomes; other studies using calcium channel blockers have shown comparable results as well. On the flip side, several well-known studies, including the Appropriate Blood Pressure Control in Diabetes (ABCD) trial, the Captopril Prevention Project (CPP), and the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET) suggest improved cardiovascular outcomes with the specific use of ACE inhibitors as first-line therapy (Chapter 63). Based on currently available evidence, ACE inhibitors are recommended as first-line antihypertensive therapy in patients with diabetes, especially in the presence of microalbuminuria or overt nephropathy. Angiotensin II receptor antagonists are an excellent alternative, especially in patients who are unable to tolerate ACE inhibitors.

Dyslipidemia is another crucial therapeutic target in the management of diabetes. The most common lipid disorder associated with diabetes is an increased level of triglyceride-rich lipoproteins (e.g., very low density lipoprotein); depressed levels of high-density lipoprotein are also common, as are the presence of "small dense" atherogenic low-density lipoprotein molecules. The third report of the National Cholesterol Education Program (NCEP) Expert Panel continues to identify low-density lipoprotein cholesterol as the primary target for therapy, based on overwhelming evidence from clinical trials. This panel has recently established diabetes as a coronary heart disease "equivalent," meaning that all diabetic patients should strive for low-density lipoprotein levels below 100 mg/dL; high-density lipoprotein levels should exceed 40 mg/dL in men and 50 mg/dL in women, while triglyceride levels should fall below 200 mg/dL (ideally, below 150 mg/dL). Initial steps in treating diabetic dyslipidemia should include optimization of glycemic control, dietary reinforcement, and a prescription of aerobic exercise. Strict dietary parameters for diabetic patients with dyslipidemia call for less than 35% of daily calories as fat, with less than 7% of total calories as saturated fat and less than 200 mg/day of dietary cholesterol (the NCEP Step II diet). Regular aerobic exercise helps by raising high-density lipoprotein levels, and weight loss achieved through exercise can further attenuate lipid abnormalities.

Hydroxymethylglutaryl coenzyme A reductase inhibitors (i.e., "statins") are generally used first-line for lowering low-density lipoprotein cholesterol in patients with diabetes; of note, many of the statins have a modest triglyceride-lowering effect as well. Controlled trials specifically document the beneficial effect of statins on patients with diabetes, even in the absence of coronary disease. If statins are contraindicated, or poorly tolerated, the cholesterol absorption inhibitor ezetimibe or bile acid sequestrants are an alternative means of lowering low-density lipoprotein. Bile acid sequestrants, however, can actually raise triglyceride levels and should therefore be used with caution. Nicotinic acid, while also effective at lowering low-density lipoprotein (and triglycerides), is less useful in diabetic patients, since it can worsen insulin resistance and adversely affect glycemic control. Low-density lipoprotein, of

course, is not the only appropriate target for lipid-lowering therapy. Recent prospective trials using fibric acid derivatives (e.g., gemfibrozil, fenofibrate) to lower triglyceride levels and raise high-density lipoprotein have also produced substantially improved cardiovascular outcomes.

The measures described are largely aimed at preventing coronary artery disease in diabetic patients; once coronary artery disease has been established, it should also be aggressively treated. Compared to the general population, a higher proportion of diabetic patients die within a year of an acute myocardial infarction. Furthermore, while there has recently been a considerable decline in overall coronary artery disease–related mortality, a similar decline in patients with diabetes has not been observed. Low-dose aspirin therapy (81 to 325 mg/day) should be routinely recommended for the majority of adult patients with diabetes (especially with concurrent CAD), because of proven reductions in cardiovascular morbidity and mortality. After myocardial infarction, particularly in the setting of left ventricular systolic dysfunction, β-blockers and ACE inhibitors (or angiotensin II receptor blockers) may offer additional benefits. Finally, although angioplasty is an option in diabetic patients with coronary disease, there is evidence to suggest that diabetic patients may derive greater-than-expected comparative benefit from coronary bypass procedures. With the recent development of advanced stenting procedures and adjunctive antiplatelet therapy, however, this distinction may become less important in the future.

Unfortunately, the known association between diabetes mellitus and premature atherosclerosis may only be the "tip of the iceberg" with regard to linking glucose metabolism and vascular risk. Insulin resistance (i.e., impaired insulin-stimulated glucose metabolism) is quite common in "healthy" people living in Western nations; in such individuals, insulin resistance is often counterbalanced by increased insulin secretion, preventing the emergence of overt diabetes mellitus. Although this state of chronic hyperinsulinemia may successfully defend against diabetes, a heavy price may be paid; compensatory hyperinsulinemia has been postulated to have adverse effects on other insulin-related systems, such as sympathetic nervous system activity, renal sodium reabsorption, hepatic triglyceride synthesis, and arterial smooth muscle proliferation. This much is known: nonobese, nondiabetic individuals with insulin resistance and hyperinsulinemia have higher blood pressure, glucose levels, and triglyceride levels (and lower high-density lipoprotein cholesterol concentrations) than matched subjects with normal insulin levels. The term *metabolic syndrome* (formerly known as "syndrome X") was coined to describe this phenomenon, namely, the clustering within one person of hyperinsulinemia, centrally distributed adiposity, mild glucose intolerance, dyslipidemia, and hypertension, each of which is likely an independent risk factor for atherosclerosis (Fig. 242–12). Prospective population studies have confirmed that chronic hyperinsulinemia predicts the development of cardiovascular disease. Although such statistical associations do not prove causality, they suggest that insulin resistance itself may play a role in promoting atherosclerosis. If true, this hypothesis further underscores the importance of lifestyle changes in the treatment of patients with more subtle metabolic abnormalities (i.e., metabolic syndrome, impaired glucose tolerance, and/or impaired fasting glucose).

An important final note: concerns about hyperinsulinemia should *not* be interpreted as a signal to reduce therapeutic insulin doses, because the long-term adverse effects of poor glycemic control are undoubtedly much greater than those possibly caused by hyperinsulinemia. This point is clearly supported by the UKPDS, in which intensive treatment with insulin or sulfonylureas tended to reduce cardiovascular events despite inducing hyperinsulinemia. Treatment of impaired glucose tolerance with the α-glucosidase inhibitor acarbose is a promising new approach for reducing hypertension and cardiovascular events in patients with impaired glucose tolerance.

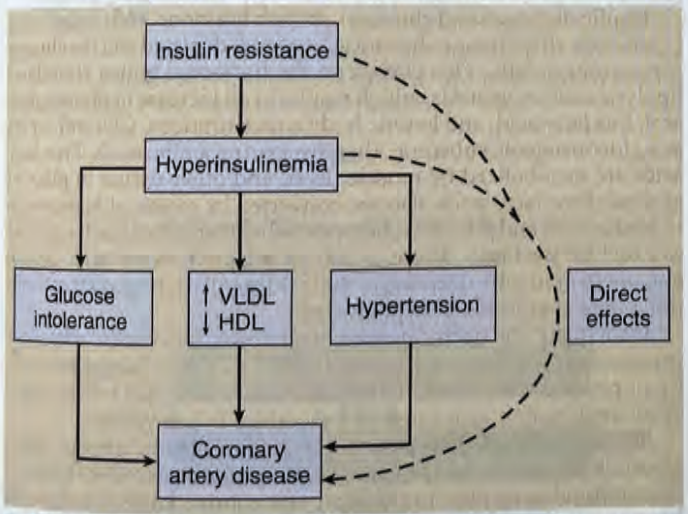

FIGURE 242–12 • The metabolic syndrome. Insulin resistance may account for a clustering of cardiovascular risk factors, including hypertension, dyslipidemia, and syndromes of glucose intolerance. HDL = high-density lipoprotein; VLDL = very low density lipoprotein.

Table 242–12 • KEY ELEMENTS OF A COMPREHENSIVE MANAGEMENT PLAN FOR PATIENTS WITH DIABETES MELLITUS

Lifestyle changes
Proper diet
Aerobic exercise
Weight control
Smoking cessation
Control of modifiable metabolic factors
Glucose control
Lipid control
Blood pressure control
Aspirin ("thrombotic control")
Preventive care
Regular medical/neurologic screening exams
Regular screening for albuminuria
Regular ophthalmologic examinations
Regular podiatric examinations (and self-examinations)
Regular dental check-ups

Summary

In caring for patients with diabetes mellitus, the primary long-term goals are to minimize complications and to preserve the patients' sense of clinical well-being. These goals are attained most easily through early detection and treatment, perhaps even before the patient meets formal diagnostic criteria. In view of the wide array of problems encountered in diabetes, patient care must be thorough and comprehensive and involves far more than simple glycemic control. Lifestyle modification should be the primary focus of patient care, and special attention should be devoted to concurrent risk factors that compound the adverse effects of diabetes on atherogenesis and cardiovascular disease. Lastly, because most complications of diabetes develop slowly and are not easily reversible, it is crucial for clinicians to take a prospective, preventive approach to diabetes care. Key elements of a comprehensive management plan for the care of diabetic patients are summarized in Table 242–12.

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243 HYPOGLYCEMIA/PANCREATIC ISLET CELL DISORDERS

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HYPOGLYCEMIA

Hypoglycemia is a clinical syndrome of diverse causes in which low levels of plasma glucose eventually lead to neuroglycopenia.

Regulation of Carbohydrate Metabolism

INTERACTIONS BETWEEN INSULIN AND COUNTER-INSULIN HORMONES. Under normal circumstances, plasma glucose concentration averages 70 to 100 mg/dL before meals and rarely exceeds 140 to 150 mg/dL after meals. The brain is almost totally dependent on glucose for energy, although over the long term it can adapt to substrates other than glucose (e.g., ketone bodies). Because severe hypoglycemia can impair mental function and, if prolonged, can cause permanent brain damage, a series of well-developed, and at times redundant, homeostatic processes defend against hypoglycemia. Insulin suppresses glucose production by inhibiting both glycogenolysis and gluconeogenesis. Insulin also stimulates glucose uptake in muscle, liver, and fat. Glucagon, epinephrine, cortisol, and growth hormone, collectively referred to as the counter-regulatory or counter-insulin hormones, oppose the effects of insulin.

In healthy nondiabetic subjects, insulin concentration increases as glucose concentration increases and falls as glucose concentration falls. In contrast, counter-regulatory hormone concentrations change (in general) in the opposite direction of insulin, falling as glucose rises and rising as glucose falls. By doing so, insulin and the counter-insulin hormones act in concert to ensure that the amount of glucose entering and leaving the blood stream is closely matched in both the fed and the fasted state. Excess amounts of insulin or insulin-like material (e.g., insulin-like growth factor [IGF]-1 or IGF-2), inadequate secretion of counter-insulin hormones, insufficient substrate, or defects in the gluconeogenic or glycogenolytic pathways alone or in combination can disrupt this balance and cause hypoglycemia.

REGULATION OF GLUCOSE CONCENTRATION IN THE FED STATE. After an overnight fast (e.g., 8 to 10 hours), rates of glucose production and utilization average about 2 mg/kg/min. At this time, the majority of the glucose is released from the liver, with a small amount being produced by the kidney. Carbohydrate ingestion increases glucose concentration, which stimulates secretion of insulin from the pancreatic β cells and suppresses secretion of glucagon from the pancreatic α cells. The resultant rise in the insulin-to-glucagon ratio increases hepatic glycogen synthesis and inhibits both glycogenolysis and gluconeogenesis, thereby resulting in a increase in hepatic glycogen content. Glucose concentrations continue to rise until the rate of glucose uptake by peripheral tissues exceeds the net amount of glucose (meal-derived and endogenously produced) being released from the splanchnic bed. Glucose concentration then begins to fall toward preprandial levels. This results in a progressive fall in insulin and a progressive rise in glucagon concentrations, which in turn permits a gradual increase in endogenous glucose production and a gradual fall in glucose utilization to basal rates. Depending on the amount and type of food ingested, both glucose concentration and turnover are generally back to basal levels sometime between 4 and 6 hours after the start of a meal.

Thus, the rate of carbohydrate absorption, the timing as well as the amount of insulin and glucagon secreted, the ability of the liver to store and subsequently release glucose, and the response of the liver, muscle, and fat to insulin and counter-insulin hormones all interact to minimize the rise in glucose concentration after a meal as well as to ensure a smooth return of glucose concentrations to preprandial levels during the transition from the fed to the postabsorptive state.

REGULATION OF GLUCOSE CONCENTRATIONS IN THE FASTED STATE. The contribution of gluconeogenesis becomes progressively more important as the duration of fast is extended and hepatic glycogen stores are depleted. The rate of glycogen depletion depends on a variety of factors, including antecedent diet and exercise, but is nearly complete after 24 to 48 hours of fasting. Anything that lowers the demand for glucose lessens the need to break down protein stores. This is accomplished by changing from a primarily carbohydrate-based metabolism in the fed state to a primarily fat-based metabolism in the fasted state.

Insulin decreases and glucagon, growth hormone, and cortisol concentrations all increase as hepatic glycogen is depleted and the glucose concentration falls. This change in the hormonal milieu stimulates lipolysis and ketogenesis, which results in an increase in plasma glycerol, free fatty acid, and ketone body concentrations. Glycerol serves as a gluconeogenic substrate, thereby sparing amino acids. Free fatty acids are metabolized by muscle, liver, and other tissues in place of glucose. Free fatty acids also are converted by means of ketogenesis to acetoacetate and β-hydroxybutyrate, which can substitute for glucose as a fuel for the brain. These metabolic adaptations normally permit glucose to gradually decrease to 40 to 50 mg/dL during a fast without provoking symptoms of hypoglycemia.

Inadequate glycogen stores or breakdown, insufficient gluconeogenesis due to defects in enzyme activity, lack of substrate availability, or persistent elevations of insulin or of insulin-like activity, alone or in combination, can cause or exacerbate hypoglycemia.

RECOVERY FROM HYPOGLYCEMIA. If counter-regulation is intact, hypoglycemia (regardless of the cause) will result in a decrease in insulin secretion and an increase in glucagon, epinephrine, cortisol, and growth hormone secretion. Glucagon provides the major defense against acute hypoglycemia. Epinephrine appears to become progressively more important when hypoglycemia is prolonged or severe. Permissive amounts of cortisol and growth hormone are required for a normal hepatic response to glucagon and epinephrine. Drugs or diseases that inhibit counter-regulatory secretion or action predispose to hypoglycemia.

Clinical Manifestations

Symptoms of hypoglycemia have been classified into two major groups: those arising from activation of the autonomic nervous system (autonomic) and those related to insufficient glucose supply to the brain (neuroglycopenic).

During acute insulin-induced hypoglycemia in healthy persons, autonomic symptoms are recognized at a threshold of approximately 60 mg/dL (3 mM) and impairment of brain function manifested by neuroglycopenic symptoms occurs at a threshold of approximately 50 mg/dL (2.8 mM) in arterialized venous blood (Fig. 243–1). Comparable venous levels would be about 3 mg/dL