17th Edition

HARRISON'S Principles of INTERNAL MEDICINE

EDITORS

Anthony S. Fauci, MD
Chief, Laboratory of Immunoregulation; Director,
National Institute of Allergy and Infectious Diseases,
National Institutes of Health, Bethesda

Eugene Braunwald, MD
Distinguished Hersey Professor of Medicine,
Harvard Medical School; Chairman, TIMI Study Group,
Brigham and Women's Hospital, Boston

Dennis L. Kasper, MD
William Ellery Channing Professor of Medicine,
Professor of Microbiology and Molecular Genetics,
Harvard Medical School; Director, Channing Laboratory,
Department of Medicine, Brigham and Women's Hospital, Boston

Stephen L. Hauser, MD
Robert A. Fishman Distinguished Professor and Chairman,
Department of Neurology, University of California,
San Francisco, San Francisco

Dan L. Longo, MD
Scientific Director, National Institute on Aging,
National Institutes of Health, Bethesda and Baltimore

J. Larry Jameson, MD, PhD
Professor of Medicine;
Vice-President for Medical Affairs and Lewis Landsberg Dean,
Northwestern University Feinberg School of Medicine, Chicago

Joseph Loscalzo, MD, PhD
Hersey Professor of the Theory and Practice of Medicine,
Harvard Medical School; Chairman, Department of Medicine;
Physician-in-Chief, Brigham and Women's Hospital, Boston

Mc Graw Hill Medical

New York Chicago San Francisco Lisbon London Madrid Mexico City
New Delhi San Juan Seoul Singapore Sydney Toronto

Note: Dr. Fauci's and Dr. Longo's works as editors and authors were performed outside the scope of their employment as U.S. government employees. These works represent their personal and professional views and not necessarily those of the U.S. government.

Harrison's
PRINCIPLES OF INTERNAL MEDICINE
Seventeenth Edition

1234567890 DOWDOW 098

Single Edition Set ISBN 978-0-07-146633-2; MHID 0-07-146633-9
Single Edition Book ISBN 978-0-07-159991-7; MHID 0-07-159991-6

Two Volume Set ISBN 978-0-07-147691-1; MHID 0-07-147691-1
Volume 1 ISBN 978-0-07-147692-8; MHID 0-07-147692-X
Volume 2 ISBN 978-0-07-147693-5; MHID 0-07-147693-8

DVD ISBN 978-0-07-159990-0; MHID 0-07-159990-8

FOREIGN LANGUAGE EDITIONS

Arabic (13e): McGraw-Hill Libri Italia srl (1996)
Chinese Long Form (15e): McGraw-Hill International Enterprises, Inc., Taiwan
Chinese Short Form (15e): McGraw-Hill Education (Asia), Singapore
Croatian (16e): Placebo, Split, Croatia
French (16e): Medecine-Sciences Flammarion, Paris, France
German (16e): ABW Wissenschaftsverlagsgesellschaft mbH, Berlin, Germany
Greek (16e): Parissianos, S.A., Athens, Greece
Italian (16e): The McGraw-Hill Companies, Srl, Milan, Italy
Japanese (16e): MEDSI-Medical Sciences International Ltd, Tokyo, Japan
Korean (16e): McGraw-Hill Korea, Inc., Seoul, Korea
Polish (14e): Czelej Publishing Company, Lubin, Poland (2000)
Portuguese (16e): McGraw-Hill Interamericana do Brazil, Rio de Janeiro, Brazil
Romanian (14e): Teora Publishers, Bucharest, Romania (2000)
Serbian (15e): Publishing House Romanov, Bosnia & Herzegovina, Republic of Serbska
Spanish (16e): McGraw-Hill Interamericana de Espana S.A., Madrid, Spain
Turkish (15e): Nobel Tip Kitabevleri, Ltd., Istanbul, Turkey
Vietnamese (15e): McGraw-Hill Education (Asia), Singapore

This book was set in Minion, Myriad, and Dax by Silverchair Science + Communications, Inc. The editors were James Shanahan and Mariapaz Ramos Englis; editorial assistant was Jenna Esposito. The production director was Phil Galea and production manager was Catherine Saggese. The index was prepared by Barbara Littlewood. The text designer was Alan Barnett of alan barnett design; cover design was by David Dell'Accio. The medical illustrator was Daniel Knopsnyder.

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

Library of Congress Cataloging-in-Publication Data

Harrison's principles of internal medicine. -- 17th ed. / editors, Anthony S. Fauci ... [et al.].
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-07-146633-2 (hardcover : v. 2 : alk. paper)
ISBN-10: 0-07-146633-9 (hardcover : v. 2 : alk. paper)
ISBN-13: 978-0-07-147691-1 (hardcover : set : v. 2 : alk. paper)
ISBN-10: 0-07-147691-1 (hardcover : set : v. 2 : alk. paper) 1. Internal medicine. I. Fauci, Anthony S., II. Title: Principles of internal medicine.
[DNLM: 1. Internal Medicine. WB 115 H322 2008]
RC46.H333 2008
616--dc22

2007012181

TABLE 73-10 ENTERAL FORMULAS

Composition Characteristics	Clinical Indications
Standard Enteral Formula	
1. Complete dietary products (+)[a] a. Caloric density 1 kcal/mL b. Protein ~14% cals, caseinates, soy, lactalbumin c. CHO ~60% cals, hydrolyzed corn starch, maltodextrin, sucrose d. Fat ~30% cals, corn, soy, safflower oils e. Recommended daily intake of all minerals and vitamins in >1500 kcal/d f. Osmolality (mosmol/kg): ~300	Suitable for most patients requiring tube feeding; some can be used orally
Modified Enteral Formulas	
1. Caloric density 1.5–2 kcal/mL (+)	Fluid-restricted patients
2. a. High protein ~20–25% protein (+)	Critically ill patients
b. Hydrolyzed protein to small peptides (+)	Impaired absorption
c. ↑ Arginine, glutamine, nucleotides, ω3 fat (+++)	Immune-enhancing diets
d. ↑ Branched-chain amino acids, ↓ aromatic amino acids (+++)	Liver failure patients intolerant of 0.8 g/kg protein
e. Low protein of high biologic value	Renal failure patient for brief periods if critically ill
3. a. Low fat, partial MCT substitution (+)	Fat malabsorption
b. ↑ Fat >40% cals (++)	Pulmonary failure with CO_2 retention on standard formula, limited utility
c. ↑ Fat from MUFA (++)	Improvement in glycemic index control in diabetes
d. ↑ Fat from ω3 and ↓ ω6 linoleic acid (+++)	Improved ventilation in ARDS
4. Fiber provided as soy polysaccharide (+)	Improved laxation

Cost: + inexpensive; ++ moderately expensive; +++ very expensive.
Note: ARDS, acute respiratory distress syndrome; CHO, carbohydrate; MCT, medium-chain triglyceride; MUFA, monounsaturated fatty acids; ω3 or ω6, polyunsaturated fat with first double bond at carbon 3 (fish oils) or carbon 6 (vegetable oils).
Source: Adapted from chapter in *Harrison's Principles of Internal Medicine*, 16e, by Lyn Howard, MD.

using nurse-directed algorithms for formula advancement, combining enteral with parenteral feeding, and using post–ligament of Treitz feeding. Tube feeding should not be discontinued for gastric residuals of <300 mL unless there are other signs of gastrointestinal intolerance such as nausea, vomiting, or abdominal distention. Continuous feeding using pumps is better tolerated intragastrically and is essential for feeding into the jejunum. For small-bowel feeding, residuals are not assessed but abdominal pain and distention should be monitored.

Diarrhea Enteral feeding often leads to diarrhea, especially if bowel function is compromised by disease or drugs, particularly broad-spectrum antibiotics. Diarrhea may be controlled by the use of a continuous drip, with a fiber-containing formula, or by adding an antidiarrheal agent to the formula. However, *Clostridium difficile*, which is a common cause of diarrhea in patients being tube fed, should be ruled out before using antidiarrheal agents. H2 blockers may also assist in reducing the net fluid presented to the colon. Diarrhea associated with enteral feeding does not necessarily imply inadequate absorption of nutrients other than water and electrolytes. Amino acids and glucose are particularly well absorbed in the upper small bowel except in the most diseased or shortest bowel. Since luminal nutrients exert trophic effects on the gut mucosa, it is often appropriate to persist with tube feeding, despite the diarrhea, even when this necessitates supplemental parenteral fluid support.

ACKNOWLEDGMENT

The authors acknowledge the contributions of Lyn Howard, MD, the author in earlier editions of HPIM, to material in this chapter.

FURTHER READINGS

AUGUST D et al: Evidence-based approach to optimal management of HPEN access. J Parenter Enteral Nutr 30:S5, 2006

BISTRIAN B, MCCOWEN K: Nutritional support in the adult intensive care unit: Key controversies. Crit Care Med 34:1525, 2006

CENTERS FOR DISEASE CONTROL AND PREVENTION: Reduction in central line–associated bloodstream infections among patients in intensive care units—Pennsylvania, April 2001–March 2005. MMWR 54:1013, 2005

DEBAVEYE Y, VAN DEN BERGHE G: Risks and benefits of nutritional support during critical illness. Annu Rev Nutr 26:513, 2006

KORETZ RL et al: Does enteral nutrition affect clinical outcome? A systematic review of the randomized trials. Am J Gastroenterol 102(2):412, 2007

MILNE A et al: Meta-analysis: Protein and energy supplementation in older people. Ann Intern Med 144:37, 2006

PLANK LD, HILL GL: Energy balance in critical illness. Proc Nutr Soc 62:545, 2003

SIMPSON F, DOIG GS: Parenteral vs. enteral nutrition in the critically ill patient: A meta-analysis of trials using the intention to treat principle. Intensive Care Med 31:12, 2005

VAN DEN BERGHE G et al: Intensive insulin therapy in the critically ill patients. N Engl J Med 345:1359, 2001

74 Biology of Obesity

Jeffrey S. Flier, Eleftheria Maratos-Flier

In a world where food supplies are intermittent, the ability to store energy in excess of what is required for immediate use is essential for survival. Fat cells, residing within widely distributed adipose tissue depots, are adapted to store excess energy efficiently as triglyceride and, when needed, to release stored energy as free fatty acids for use at other sites. This physiologic system, orchestrated through endocrine and neural pathways, permits humans to survive starvation for as long as several months. However, in the presence of nutritional abundance and a sedentary lifestyle, and influenced importantly by genetic endowment, this system increases adipose energy stores and produces adverse health consequences.

DEFINITION AND MEASUREMENT

Obesity is a state of excess adipose tissue mass. Although often viewed as equivalent to increased body weight, this need not be the case—lean but very muscular individuals may be overweight by numerical standards without having increased adiposity. Body weights are distributed continuously in populations, so that choice of a medically meaningful distinction between lean and obese is somewhat arbitrary. Obesity is therefore more effectively defined by assessing its linkage to morbidity or mortality.

Although not a direct measure of adiposity, the most widely used method to gauge obesity is the *body mass index* (BMI), which is equal to weight/height^2 (in kg/m^2) (Fig. 74-1). Other approaches to quantifying obesity include anthropometry (skin-fold thickness), densitometry (underwater weighing), CT or MRI, and electrical impedance. Using data from the Metropolitan Life Tables, BMIs for the midpoint of all heights and frames among both men and women range from 19–26 kg/m^2; at a similar BMI, women have more body fat than men. Based on data of substantial morbidity, a BMI of 30 is most commonly used as a threshold for obesity in both men and women. Large-scale epidemiologic studies suggest that all-cause, metabolic, cancer, and cardiovascular morbidity begin to rise (albeit at a slow rate) when BMIs are ≥ 25, suggesting that the cut-off for obesity should be low-

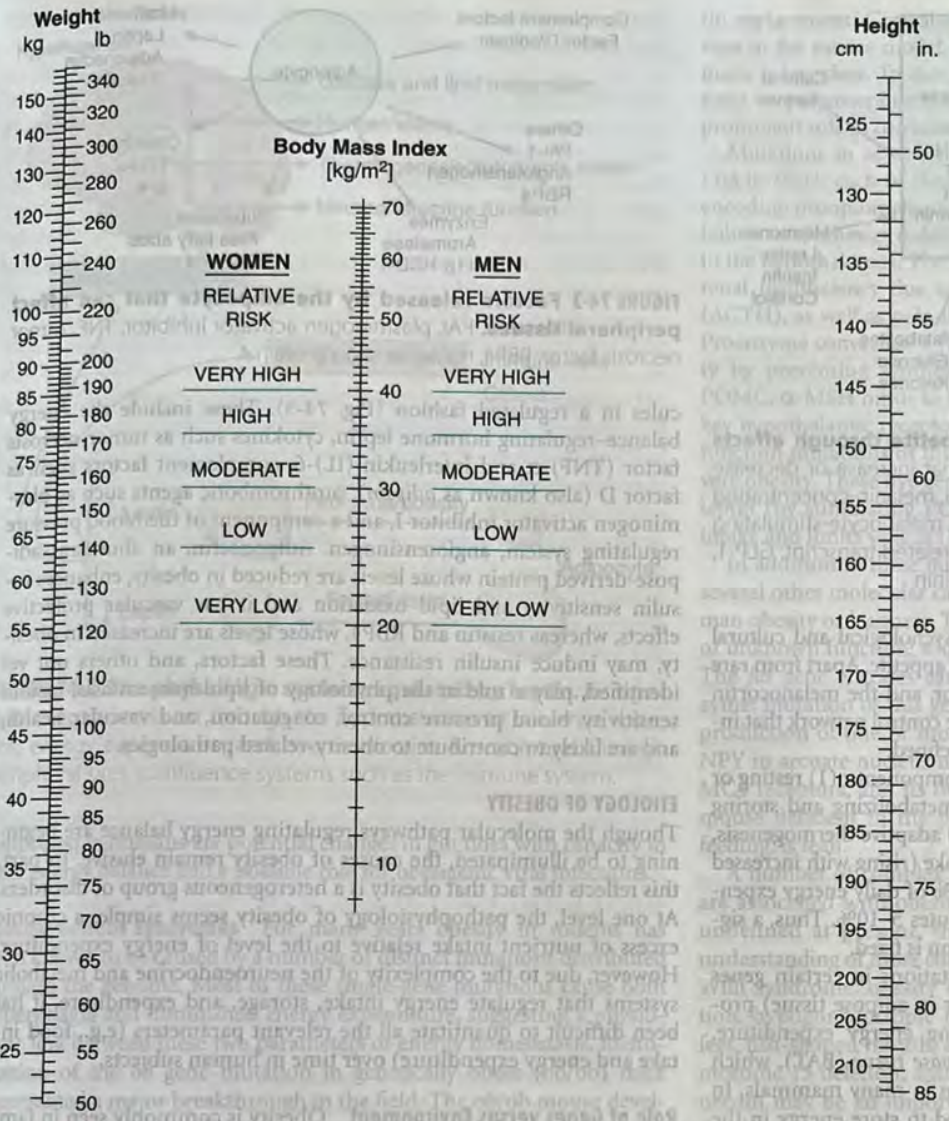


FIGURE 74-1 Nomogram for determining body mass index. To use this nomogram, place a ruler or other straight edge between the body weight (without clothes) in kilograms or pounds located on the left-hand line and the height (without shoes) in centimeters or inches located on the right-hand line. The body mass index is read from the middle of the scale and is in metric units. *(Copyright 1979, George A. Bray, M.D.; used with permission.)*

ered. Most authorities use the term *overweight* (rather than obese) to describe individuals with BMIs between 25 and 30. A BMI between 25 and 30 should be viewed as medically significant and worthy of therapeutic intervention, especially in the presence of risk factors that are influenced by adiposity, such as hypertension and glucose intolerance.

The distribution of adipose tissue in different anatomic depots also has substantial implications for morbidity. Specifically, intraabdominal and abdominal subcutaneous fat have more significance than subcutaneous fat present in the buttocks and lower extremities. This distinction is most easily made clinically by determining the waist-to-hip ratio, with a ratio >0.9 in women and >1.0 in men being abnormal. Many of the most important complications of obesity, such as insulin resistance, diabetes, hypertension, hyperlipidemia, and hyperandrogenism in women, are linked more strongly to intraabdominal and/or upper body fat than to overall adiposity (Chap. 236). The mechanism underlying this association is unknown but may relate to the fact that intraabdominal adipocytes are more lipolytically active than those from other depots. Release of free fatty acids into the portal circulation has adverse metabolic actions, especially on the liver. Whether adipokines and cytokines secreted by visceral adipocytes play an additional role in systemic complications of obesity is an area of active investigation.

PREVALENCE

Data from the National Health and Nutrition Examination Surveys (NHANES) show that the percent of the American adult population with obesity (BMI > 30) has increased from 14.5% (between 1976 and 1980) to 30.5% (between 1999 and 2000). As many as 64% of U.S. adults ≥20 years of age were overweight (defined as BMI > 25) between the years of 1999 and 2000. Extreme obesity (BMI ≥40) has also increased and affects 4.7% of the population. The increasing prevalence of medically significant obesity raises great concern. Obesity is more common among women and in the poor; the prevalence in children is also rising at a worrisome rate.

PHYSIOLOGIC REGULATION OF ENERGY BALANCE

Substantial evidence suggests that body weight is regulated by both endocrine and neural components that ultimately influence the effector arms of energy intake and expenditure. This complex regulatory system is necessary because even small imbalances between energy intake and expenditure will ultimately have large effects on body weight. For example, a 0.3% positive imbalance over 30 years would result in a 9-kg (20-lb) weight gain. This exquisite regulation of energy balance cannot be monitored easily by calorie-counting in relation to physical activity. Rather, body weight regulation or dysregulation depends on a complex interplay of hormonal and neural signals. Alterations in stable weight by forced overfeeding or food deprivation induce physiologic changes that resist these perturbations: with weight loss, appetite increases and energy expenditure falls; with overfeeding, appetite falls and energy expenditure increases. This latter compensatory mechanism frequently fails, however, permitting obesity to develop when food is abundant and physical activity is limited. A major regulator of these adaptive responses is the adipocyte-derived hormone leptin, which acts through brain circuits (predominantly in the hypothalamus) to influence appetite, energy expenditure, and neuroendocrine function (see below).

Appetite is influenced by many factors that are integrated by the brain, most importantly within the hypothalamus (Fig. 74-2). Signals that impinge on the hypothalamic center include neural afferents, hormones, and metabolites. Vagal inputs are particularly important, bringing information from viscera, such as gut distention. Hormonal signals include leptin, insulin, cortisol, and gut peptides. Among the latter are ghrelin, which is made in the stomach and stimulates feeding, and peptide YY (PYY) and cholecystokinin, which are made in the small intestine and signal to the brain through direct action on hypothalamic control centers and/or via the vagus nerve. Metabolites, including glucose, can influence appetite, as seen by the effect of hypoglycemia to induce hunger; however, glucose is not normally a major regulator of appetite. These diverse hormonal, metabolic, and neural signals act by influencing the expression and release of various hypothalamic peptides [e.g., neuropeptide Y (NPY), Agouti-related peptide (AgRP), α-melanocyte-stimulating hormone (α-MSH), and melanin-concentrating hormone (MCH)] that are integrated with serotonergic, catecholaminergic, endocannabinoid,

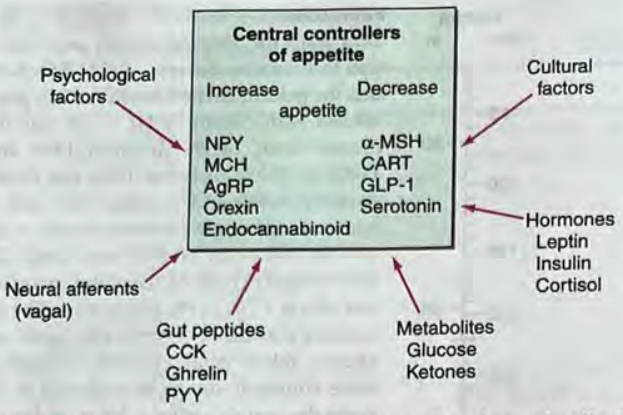


FIGURE 74-2 The factors that regulate appetite through effects on central neural circuits. Some factors that increase or decrease appetite are listed. NPY, neuropeptide Y; MCH, melanin-concentrating hormone; AgRP, Agouti-related peptide; MSH, melanocyte-stimulating hormone; CART, cocaine- and amphetamine-related transcript; GLP-1, glucagon-related peptide-1; CCK, cholecystokinin.

and opioid signaling pathways (see below). Psychological and cultural factors also play a role in the final expression of appetite. Apart from rare genetic syndromes involving leptin, its receptor, and the melanocortin system, specific defects in this complex appetite control network that influence common cases of obesity are not well defined.

Energy expenditure includes the following components: (1) resting or basal metabolic rate; (2) the energy cost of metabolizing and storing food; (3) the thermic effect of exercise; and (4) adaptive thermogenesis, which varies in response to chronic caloric intake (rising with increased intake). Basal metabolic rate accounts for ~70% of daily energy expenditure, whereas active physical activity contributes 5–10%. Thus, a significant component of daily energy consumption is fixed.

Genetic models in mice indicate that mutations in certain genes (e.g., targeted deletion of the insulin receptor in adipose tissue) protect against obesity, apparently by increasing energy expenditure. Adaptive thermogenesis occurs in *brown adipose tissue* (BAT), which plays an important role in energy metabolism in many mammals. In contrast to white adipose tissue, which is used to store energy in the form of lipids, BAT expends stored energy as heat. A mitochondrial *uncoupling protein* (UCP-1) in BAT dissipates the hydrogen ion gradient in the oxidative respiration chain and releases energy as heat. The metabolic activity of BAT is increased by a central action of leptin, acting through the sympathetic nervous system, which heavily innervates this tissue. In rodents, BAT deficiency causes obesity and diabetes; stimulation of BAT with a specific adrenergic agonist (β_3 agonist) protects against diabetes and obesity. Although BAT exists in humans (especially neonates), its physiologic role is not yet established. Homologues of UCP-1 (UCP-2 and -3) may mediate uncoupled mitochondrial respiration in other tissues.

THE ADIPOCYTE AND ADIPOSE TISSUE

Adipose tissue is composed of the lipid-storing adipose cell and a stromal/vascular compartment in which cells including preadipocytes and macrophages reside. Adipose mass increases by enlargement of adipose cells through lipid deposition, as well as by an increase in the number of adipocytes. Obese adipose tissue is also characterized by increased numbers of infiltrating macrophages. The process by which adipose cells are derived from a mesenchymal preadipocyte involves an orchestrated series of differentiation steps mediated by a cascade of specific transcription factors. One of the key transcription factors is *peroxisome proliferator-activated receptor* γ (PPARγ), a nuclear receptor that binds the thiazolidinedione class of insulin-sensitizing drugs used in the treatment of type 2 diabetes (Chap. 338).

Although the adipocyte has generally been regarded as a storage depot for fat, it is also an endocrine cell that releases numerous molecules in a regulated fashion (Fig. 74-3). These include the energy balance–regulating hormone leptin, cytokines such as tumor necrosis factor (TNF) α and interleukin (IL)-6, complement factors such as factor D (also known as *adipsin*), prothrombotic agents such as plasminogen activator inhibitor I, and a component of the blood pressure regulating system, angiotensinogen. Adiponectin, an abundant adipose-derived protein whose levels are reduced in obesity, enhances insulin sensitivity and lipid oxidation and it has vascular protective effects, whereas resistin and RBP4, whose levels are increased in obesity, may induce insulin resistance. These factors, and others not yet identified, play a role in the physiology of lipid homeostasis, insulin sensitivity, blood pressure control, coagulation, and vascular health, and are likely to contribute to obesity-related pathologies.

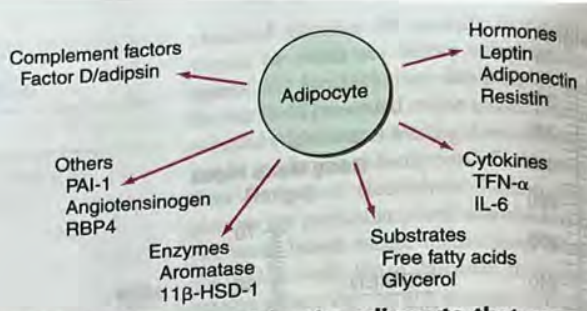


FIGURE 74-3 Factors released by the adipocyte that can affect peripheral tissues. PAI, plasminogen activator inhibitor; TNF, tumor necrosis factor; RBP4, retinal binding protein 4.

ETIOLOGY OF OBESITY

Though the molecular pathways regulating energy balance are beginning to be illuminated, the causes of obesity remain elusive. In part, this reflects the fact that obesity is a heterogeneous group of disorders. At one level, the pathophysiology of obesity seems simple: a chronic excess of nutrient intake relative to the level of energy expenditure. However, due to the complexity of the neuroendocrine and metabolic systems that regulate energy intake, storage, and expenditure, it has been difficult to quantitate all the relevant parameters (e.g., food intake and energy expenditure) over time in human subjects.

Role of Genes versus Environment Obesity is commonly seen in families, and the heritability of body weight is similar to that for height. Inheritance is usually not Mendelian, however, and it is difficult to distinguish the role of genes and environmental factors. Adoptees more closely resemble their biologic than adoptive parents with respect to obesity, providing strong support for genetic influences. Likewise, identical twins have very similar BMIs whether reared together or apart, and their BMIs are much more strongly correlated than those of dizygotic twins. These genetic effects appear to relate to both energy intake and expenditure.

Whatever the role of genes, it is clear that the environment plays a key role in obesity, as evidenced by the fact that famine prevents obesity in even the most obesity-prone individual. In addition, the recent increase in the prevalence of obesity in the United States is far too rapid to be due to changes in the gene pool. Undoubtedly, genes influence the susceptibility to obesity in response to specific diets and availability of nutrition. Cultural factors are also important—these relate to both availability and composition of the diet and to changes in the level of physical activity. In industrial societies, obesity is more common among poor women, whereas in underdeveloped countries, wealthier women are more often obese. In children, obesity correlates to some degree with time spent watching television. Although the role of diet composition in obesity continues to generate controversy, it appears that high-fat diets may promote obesity, especially when combined with diets rich in simple (as opposed to complex) carbohydrates.

Additional environmental factors may contribute to the increasing obesity prevalence. Both epidemiologic correlations and experimental data suggest that sleep deprivation leads to increased obesity. Less well

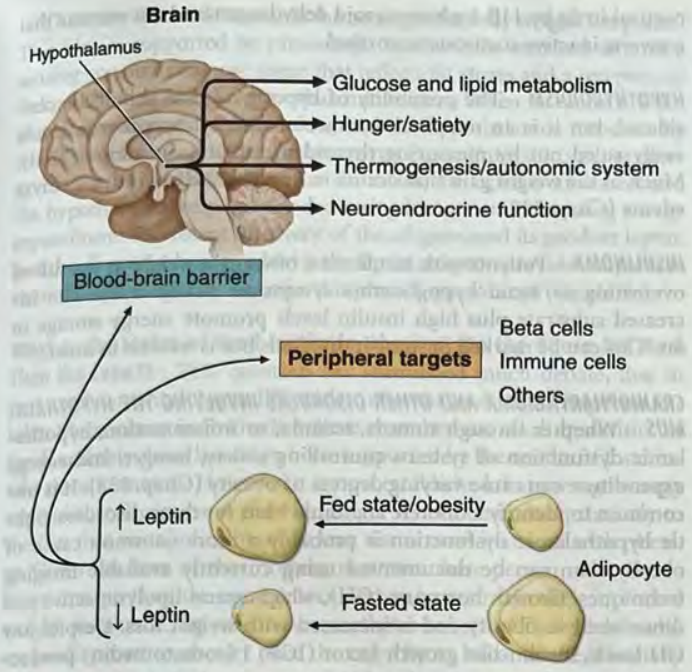


FIGURE 74-4 The physiologic system regulated by leptin. Rising or falling leptin levels act through the hypothalamus to influence appetite, energy expenditure, and neuroendocrine function and through peripheral sites to influence systems such as the immune system.

supported in humans are potential changes in gut flora with capacity to alter energy balance and a possible role for obesigenic viral infections.

Specific Genetic Syndromes For many years obesity in rodents has been known to be caused by a number of distinct mutations distributed through the genome. Most of these single-gene mutations cause both hyperphagia and diminished energy expenditure, suggesting a physiologic link between these two parameters of energy homeostasis. Identification of the *ob* gene mutation in genetically obese (ob/ob) mice represented a major breakthrough in the field. The ob/ob mouse develops severe obesity, insulin resistance, and hyperphagia, as well as efficient metabolism (e.g., it gets fat even when ingesting the same number of calories as lean litter mates). The product of the *ob* gene is the peptide leptin, a name derived from the Greek root *leptos*, meaning thin. Leptin is secreted by adipose cells and acts primarily through the hypothalamus. Its level of production provides an index of adipose energy stores (Fig. 74-4). High leptin levels decrease food intake and increase energy expenditure. Another mouse mutant, db/db, which is resistant to leptin, has a mutation in the leptin receptor and develops a similar syndrome. The *OB* gene is present in humans and expressed in fat. Several families with morbid, early-onset obesity caused by inactivating mutations in either leptin or the leptin receptor have been described, thus demonstrating the biologic relevance of leptin in humans. The obesity in these individuals begins shortly after birth, is severe, and is accompanied by neuroendocrine abnormalities. The most prominent of these is hypogonadotropic hypogonadism, which is reversed by leptin replacement. Central hypothyroidism and growth retardation are seen in the mouse model, but their occurrence in leptin-deficient humans is less clear. To date, there is no evidence to suggest that mutations or polymorphisms in the leptin or leptin receptor genes play a prominent role in common forms of obesity.

Mutations in several other genes cause severe obesity in humans (Table 74-1); each of these syndromes is rare. Mutations in the gene encoding proopiomelanocortin (POMC) cause severe obesity through failure to synthesize α-MSH, a key neuropeptide that inhibits appetite in the hypothalamus. The absence of POMC also causes secondary adrenal insufficiency due to absence of adrenocorticotropic hormone (ACTH), as well as pale skin and red hair due to absence of α-MSH. Proenzyme convertase 1 (PC-1) mutations are thought to cause obesity by preventing synthesis of α-MSH from its precursor peptide, POMC. α-MSH binds to the type 4 melanocortin receptor (MC4R), a key hypothalamic receptor that inhibits eating. Heterozygous loss-of-function mutations of this receptor account for as much as 5% of severe obesity. These five genetic defects define a pathway through which leptin (by stimulating POMC and increasing α-MSH) restricts food intake and limits weight (Fig. 74-5).

In addition to these human obesity genes, studies in rodents reveal several other molecular candidates for hypothalamic mediators of human obesity or leanness. The *tub* gene encodes a hypothalamic peptide of unknown function; mutation of this gene causes late-onset obesity. The *fat* gene encodes carboxypeptidase E, a peptide-processing enzyme; mutation of this gene is thought to cause obesity by disrupting production of one or more neuropeptides. AgRP is coexpressed with NPY in arcuate nucleus neurons. AgRP antagonizes α-MSH action at MC4 receptors, and its overexpression induces obesity. In contrast, a mouse deficient in the peptide MCH, whose administration causes feeding, is lean.

A number of complex human syndromes with defined inheritance are associated with obesity (Table 74-2). Although specific genes are undefined at present, their identification will likely enhance our understanding of more common forms of human obesity. In the Prader-Willi syndrome, obesity coexists with short stature, mental retardation, hypogonadotropic hypogonadism, hypotonia, small hands and feet, fish-shaped mouth, and hyperphagia. Most patients have a chromosome 15 deletion, and reduced expression of the signaling protein necdin may be an important cause of defective hypothalamic neural development in this disorder (Chap. 63). Bardet-Biedl syndrome

TABLE 74-1 SOME OBESITY GENES IN HUMANS AND MICE

Gene	Gene Product	Mechanism of Obesity	In Human	In Rodent
Lep (ob)	Leptin, a fat-derived hormone	Mutation prevents leptin from delivering satiety signal; brain perceives starvation	Yes	Yes
LepR (db)	Leptin receptor	Same as above	Yes	Yes
POMC	Proopiomelanocortin, a precursor of several hormones and neuropeptides	Mutation prevents synthesis of melanocyte-stimulating hormone (MSH), a satiety signal	Yes	Yes
MC4R	Type 4 receptor for MSH	Mutation prevents reception of satiety signal from MSH	Yes	Yes
AgRP	Agouti-related peptide, a neuropeptide expressed in the hypothalamus	Overexpression inhibits signal through MC4R	No	Yes
PC-1	Prohormone convertase 1, a processing enzyme	Mutation prevents synthesis of neuropeptide, probably MSH	Yes	No
Fat	Carboxypeptidase E, a processing enzyme	Same as above	No	Yes
Tub	Tub, a hypothalamic protein of unknown function	Hypothalamic dysfunction	No	Yes
TrkB	TrkB, a neurotrophin receptor	Hyperphagia due to uncharacterized hypothalamic defect	Yes	Yes

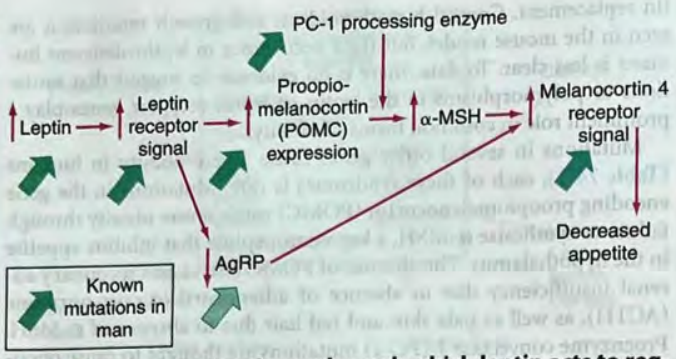


FIGURE 74-5 A central pathway through which leptin acts to regulate appetite and body weight. Leptin signals through pro-opiomelanocortin (POMC) neurons in the hypothalamus to induce increased production of α-melanocyte-stimulating hormone (α-MSH), requiring the processing enzyme PC-1 (proenzyme convertase 1). α-MSH acts as an agonist on melanocortin-4 receptors to inhibit appetite, and the neuropeptide AgRp (Agouti-related peptide) acts as an antagonist of this receptor. Mutations that cause obesity in humans are indicated by the solid green arrows.

(BBS) is a genetically heterogeneous disorder characterized by obesity, mental retardation, retinitis pigmentosa, renal and cardiac malformations, polydactyly, and hypogonadotropic hypogonadism. At least eight genetic loci have been identified, and BBS may involve defects in ciliary function.

Other Specific Syndromes Associated with Obesity • ***CUSHING'S SYNDROME*** Although obese patients commonly have central obesity, hypertension, and glucose intolerance, they lack other specific stigmata of Cushing's syndrome (Chap. 336). Nonetheless, a potential diagnosis of Cushing's syndrome is often entertained. Cortisol production and urinary metabolites (17OH steroids) may be increased in simple obesity. Unlike in Cushing's syndrome, however, cortisol levels in blood and urine in the basal state and in response to corticotropin-releasing hormone (CRH) or ACTH are normal; the overnight 1-mg dexamethasone suppression test is normal in 90%, with the remainder being normal on a standard 2-day low-dose dexamethasone suppression test. Obesity may be associated with excessive local reactivation of cortisol in fat by 11β-hydroxysteroid dehydrogenase 1, an enzyme that converts inactive cortisone to cortisol.

HYPOTHYROIDISM The possibility of hypothyroidism should be considered, but it is an uncommon cause of obesity; hypothyroidism is easily ruled out by measuring thyroid-stimulating hormone (TSH). Much of the weight gain that occurs in hypothyroidism is due to myxedema (Chap. 335).

INSULINOMA Patients with insulinoma often gain weight as a result of overeating to avoid hypoglycemic symptoms (Chap. 339). The increased substrate plus high insulin levels promote energy storage in fat. This can be marked in some individuals but is modest in most.

CRANIOPHARYNGIOMA AND OTHER DISORDERS INVOLVING THE HYPOTHALAMUS Whether through tumors, trauma, or inflammation, hypothalamic dysfunction of systems controlling satiety, hunger, and energy expenditure can cause varying degrees of obesity (Chap. 333). It is uncommon to identify a discrete anatomic basis for these disorders. Subtle hypothalamic dysfunction is probably a more common cause of obesity than can be documented using currently available imaging techniques. Growth hormone (GH), which exerts lipolytic activity, is diminished in obesity and is increased with weight loss. Despite low GH levels, insulin-like growth factor (IGF) I (somatomedin) production is normal, suggesting that GH suppression is a compensatory response to increased nutritional supply.

Pathogenesis of Common Obesity Obesity can result from increased energy intake, decreased energy expenditure, or a combination of the two. Thus, identifying the etiology of obesity should involve measurements of both parameters. However, it is nearly impossible to perform direct and accurate measurements of energy intake in free-living individuals, and the obese, in particular, often underreport intake. Measurements of chronic energy expenditure have only recently become available using doubly labeled water or metabolic chamber/rooms. In subjects at stable weight and body composition, energy intake equals expenditure. Consequently, these techniques allow assessment of energy intake in free-living individuals. The level of energy expenditure differs in established obesity, during periods of weight gain or loss, and in the pre- or postobese state. Studies that fail to take note of this phenomenon are not easily interpreted.

TABLE 74-2 A COMPARISON OF SYNDROMES OF OBESITY—HYPOGONADISM AND MENTAL RETARDATION

Feature	Syndrome				
	Prader-Willi	Laurence-Moon-Biedl	Ahlstrom	Cohen	Carpenter
Inheritance	Sporadic; two-thirds have defect	Autosomal recessive	Autosomal recessive	Probably autosomal recessive	Autosomal recessive
Stature	Short	Normal; infrequently short	Normal; infrequently short	Short or tall	Normal
Obesity	Generalized Moderate to severe Onset 1–3 yrs	Generalized Early onset, 1–2 yrs	Truncal Early onset, 2–5 yrs	Truncal Mid-childhood, age 5	Truncal, gluteal
Craniofacies	Narrow bifrontal diameter Almond-shaped eyes Strabismus V-shaped mouth High-arched palate	Not distinctive	Not distinctive	High nasal bridge Arched palate Open mouth Short philtrum	Acrocephaly Flat nasal bridge High-arched palate
Limbs	Small hands and feet Hypotonia	Polydactyly	No abnormalities	Hypotonia Narrow hands and feet	Polydactyly Syndactyly Genu valgum
Reproductive status	1° Hypogonadism	1° Hypogonadism	Hypogonadism in males but not in females	Normal gonadal function or hypogonadotrophic hypogonadism	2° Hypogonadism
Other features	Enamel hypoplasia Hyperphagia Temper tantrums Nasal speech			Dysplastic ears Delayed puberty	
Mental retardation	Mild to moderate		Normal intelligence	Mild	Slight

There is continued interest in the concept of a body weight "set point." This idea is supported by physiologic mechanisms centered around a sensing system in adipose tissue that reflects fat stores and a receptor, or "adipostat," that is in the hypothalamic centers. When fat stores are depleted, the adipostat signal is low, and the hypothalamus responds by stimulating hunger and decreasing energy expenditure to conserve energy. Conversely, when fat stores are abundant, the signal is increased, and the hypothalamus responds by decreasing hunger and increasing energy expenditure. The recent discovery of the *ob* gene, and its product leptin, and the *db* gene, whose product is the leptin receptor, provides important elements of a molecular basis for this physiologic concept (see above).

What Is the Status of Food Intake in Obesity? (Do the Obese Eat More Than the Lean?) This question has stimulated much debate, due in part to the methodologic difficulties inherent in determining food intake. Many obese individuals believe that they eat small quantities of food, and this claim has often been supported by the results of food intake questionnaires. However, it is now established that average energy expenditure increases as individuals get more obese, due primarily to the fact that metabolically active lean tissue mass increases with obesity. Given the laws of thermodynamics, the obese person must therefore eat more than the average lean person to maintain their increased weight. It may be the case, however, that a subset of individuals who are predisposed to obesity have the capacity to become obese initially without an absolute increase in caloric consumption.

What Is the State of Energy Expenditure in Obesity? The average total daily energy expenditure is higher in obese than lean individuals when measured at stable weight. However, energy expenditure falls as weight is lost, due in part to loss of lean body mass and to decreased sympathetic nerve activity. When reduced to near-normal weight and maintained there for a while, (some) obese individuals have lower energy expenditure than (some) lean individuals. There is also a tendency for those who will develop obesity as infants or children to have lower resting energy expenditure rates than those who remain lean.

The physiologic basis for variable rates of energy expenditure (at a given body weight and level of energy intake) is essentially unknown. A mutation in the human β_3-adrenergic receptor may be associated with increased risk of obesity and/or insulin resistance in certain (but not all) populations. Homologues of the BAT uncoupling protein, named UCP-2 and UCP-3, have been identified in both rodents and humans. UCP-2 is expressed widely, whereas UCP-3 is primarily expressed in skeletal muscle. These proteins may play a role in disordered energy balance.

One newly described component of thermogenesis, called *nonexercise activity thermogenesis* (NEAT), has been linked to obesity. It is the thermogenesis that accompanies physical activities other than volitional exercise, such as the activities of daily living, fidgeting, spontaneous muscle contraction, and maintaining posture. NEAT accounts for about two-thirds of the increased daily energy expenditure induced by overfeeding. The wide variation in fat storage seen in overfed individuals is predicted by the degree to which NEAT is induced. The molecular basis for NEAT and its regulation is unknown.

Leptin in Typical Obesity The vast majority of obese persons have increased leptin levels but do not have mutations of either leptin or its receptor. They appear, therefore, to have a form of functional "leptin resistance." Data suggesting that some individuals produce less leptin per unit fat mass than others or have a form of relative leptin deficiency that predisposes to obesity are at present contradictory and unsettled. The mechanism for leptin resistance, and whether it can be overcome by raising leptin levels, is not yet established. Some data suggest that leptin may not effectively cross the blood-brain barrier as levels rise. It is also apparent from animal studies that leptin signaling inhibitors, such as SOCS3 and PTP1b, are involved in the leptin-resistant state.

PATHOLOGIC CONSEQUENCES OF OBESITY

(See also Chap. 75) Obesity has major adverse effects on health. Obesity is associated with an increase in mortality, with a 50–100% increased risk of death from all causes compared to normal-weight individuals, mostly due to cardiovascular causes. Obesity and overweight together are the second leading cause of preventable death in the United States, accounting for 300,000 deaths per year. Mortality rates rise as obesity increases, particularly when obesity is associated with increased intraabdominal fat (see above). Life expectancy of a moderately obese individual could be shortened by 2–5 years, and a 20- to 30-year-old male with a BMI > 45 may lose 13 years of life. It is also apparent that the degree to which obesity affects particular organ systems is influenced by susceptibility genes that vary in the population.

Insulin Resistance and Type 2 Diabetes Mellitus Hyperinsulinemia and insulin resistance are pervasive features of obesity, increasing with weight gain and diminishing with weight loss (Chap. 236). Insulin resistance is more strongly linked to intraabdominal fat than to fat in other depots. The molecular link between obesity and insulin resistance in tissues such as fat, muscle, and liver has been sought for many years. Major factors under investigation include: (1) insulin itself, by inducing receptor downregulation; (2) free fatty acids, known to be increased and capable of impairing insulin action; (3) intracellular lipid accumulation; and (4) various circulating peptides produced by adipocytes, including the cytokines TNF-α and IL-6, RBP4, and the "adipokines" adiponectin and resistin, which are produced by adipocytes, have altered expression in obese adipocytes, and are capable of modifying insulin action. Despite nearly universal insulin resistance, most obese individuals do not develop diabetes, suggesting that the onset of diabetes requires an interaction between obesity-induced insulin resistance and other factors that predispose to diabetes, such as impaired insulin secretion (Chap. 338). Obesity, however, is a major risk factor for diabetes, and as many as 80% of patients with type 2 diabetes mellitus are obese. Weight loss and exercise, even of modest degree, are associated with increased insulin sensitivity and often improve glucose control in diabetes.

Reproductive Disorders Disorders that affect the reproductive axis are associated with obesity in both men and women. Male hypogonadism is associated with increased adipose tissue, often distributed in a pattern more typical of females. In men >160% ideal body weight, plasma testosterone and sex hormone–binding globulin (SHBG) are often reduced, and estrogen levels (derived from conversion of adrenal androgens in adipose tissue) are increased (Chap. 340). Gynecomastia may be seen. However, masculinization, libido, potency, and spermatogenesis are preserved in most of these individuals. Free testosterone may be decreased in morbidly obese men whose weight is >200% ideal body weight.

Obesity has long been associated with menstrual abnormalities in women, particularly in women with upper body obesity (Chap. 341). Common findings are increased androgen production, decreased SHBG, and increased peripheral conversion of androgen to estrogen. Most obese women with oligomenorrhea have the polycystic ovarian syndrome (PCOS), with its associated anovulation and ovarian hyperandrogenism; 40% of women with PCOS are obese. Most nonobese women with PCOS are also insulin-resistant, suggesting that insulin resistance, hyperinsulinemia, or the combination of the two are causative or contribute to the ovarian pathophysiology in PCOS in both obese and lean individuals. In obese women with PCOS, weight loss or treatment with insulin-sensitizing drugs often restores normal menses. The increased conversion of androstenedione to estrogen, which occurs to a greater degree in women with lower body obesity, may contribute to the increased incidence of uterine cancer in postmenopausal women with obesity.

Cardiovascular Disease The Framingham Study revealed that obesity was an independent risk factor for the 26-year incidence of cardiovascular disease in men and women [including coronary disease, stroke, and congestive heart failure (CHF)]. The waist/hip ratio may be the best predictor of these risks. When the additional effects of hypertension and glucose intolerance associated with obesity are included, the adverse impact of obesity is even more evident. The effect of obesity

on cardiovascular mortality in women may be seen at BMIs as low as 25. Obesity, especially abdominal obesity, is associated with an atherogenic lipid profile; with increased low-density lipoprotein (LDL) cholesterol, very low density lipoprotein, and triglyceride; and with decreased high-density lipoprotein cholesterol and decreased levels of the vascular protective adipokine adiponectin (Chap. 350). Obesity is also associated with hypertension. Measurement of blood pressure in the obese requires use of a larger cuff size to avoid artifactual increases. Obesity-induced hypertension is associated with increased peripheral resistance and cardiac output, increased sympathetic nervous system tone, increased salt sensitivity, and insulin-mediated salt retention; it is often responsive to modest weight loss.

Pulmonary Disease Obesity may be associated with a number of pulmonary abnormalities. These include reduced chest wall compliance, increased work of breathing, increased minute ventilation due to increased metabolic rate, and decreased functional residual capacity and expiratory reserve volume (Chap. 246). Severe obesity may be associated with obstructive sleep apnea and the "obesity hypoventilation syndrome" with attenuated hypoxic and hypercapnic ventilatory responses (Chap. 258). Sleep apnea can be obstructive (most common), central, or mixed and is associated with hypertension. Weight loss (10–20 kg) can bring substantial improvement, as can major weight loss following gastric bypass or restrictive surgery. Continuous positive airway pressure has been used with some success.

Gallstones Obesity is associated with enhanced biliary secretion of cholesterol, supersaturation of bile, and a higher incidence of gallstones, particularly cholesterol gallstones (Chap. 305). A person 50% above ideal body weight has about a sixfold increased incidence of symptomatic gallstones. Paradoxically, fasting increases supersaturation of bile by decreasing the phospholipid component. Fasting-induced cholecystitis is a complication of extreme diets.

Cancer Obesity in males is associated with higher mortality from cancer, including cancer of the esophagus, colon, rectum, pancreas, liver, and prostate; obesity in females is associated with higher mortality from cancer of the gallbladder, bile ducts, breasts, endometrium, cervix, and ovaries. Some of the latter may be due to increased rates of conversion of androstenedione to estrone in adipose tissue of obese individuals. It was recently estimated that obesity accounts for 14% of cancer deaths in men and 20% in women in the United States.

Bone, Joint, and Cutaneous Disease Obesity is associated with an increased risk of osteoarthritis, no doubt partly due to the trauma of added weight bearing and joint malalignment. The prevalence of gout may also be increased (Chap. 327). Among the skin problems associated with obesity is acanthosis nigricans, manifested by darkening and thickening of the skin folds on the neck, elbows, and dorsal interphalangeal spaces. Acanthosis reflects the severity of underlying insulin resistance and diminishes with weight loss. Friability of skin may be increased, especially in skin folds, enhancing the risk of fungal and yeast infections. Finally, venous stasis is increased in the obese.

FURTHER READINGS

FAROOQI IS, O'RAHILLY S: Genetics of obesity. Philos Trans R Soc Lond B Biol Sci 361:1095, 2006

FLIER JS: Obesity wars: Molecular progress confronts an expanding epidemic. Cell 116:337, 2004

KERSHAW EE, FLIER JS: Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 89:2548, 2004

MORTON GJ et al: Central nervous system control of food intake and body weight. Nature 443:289, 2006

MURPHY KG et al: Gut peptides in the regulation of food intake and energy homeostasis. Endocr Rev 27:719, 2006

OGDEN CL et al: The epidemiology of obesity. Gastroenterology 132(6):2087, 2007

OGDEN CL et al: Prevalence of overweight and obesity in the United States, 1999–2004. JAMA 295:1549, 2006

75 Evaluation and Management of Obesity

Robert F. Kushner

Over 66% of U.S. adults are currently categorized as overweight or obese, and the prevalence of obesity is increasing rapidly throughout most of the industrialized world. Based on statistics from the World Health Organization, overweight and obesity may soon replace more traditional public health concerns such as undernutrition and infectious diseases as the most significant contributors to ill health. Children and adolescents are also becoming more obese, indicating that the current trends will accelerate over time. Obesity is associated with an increased risk of multiple health problems, including hypertension, type 2 diabetes, dyslipidemia, degenerative joint disease, and some malignancies. Thus, it is important for physicians to routinely identify, evaluate, and treat patients for obesity and associated comorbid conditions.

EVALUATION

The U.S. Preventive Services Task Force recommends that physicians screen all adult patients for obesity and offer intensive counseling and behavioral interventions to promote sustained weight loss. This recommendation is consistent with previously released guidelines from the National Heart, Lung, and Blood Institute (NHLBI) and a number of medical societies. The five main steps in the evaluation of obesity are described below and include (1) focused obesity-related history, (2) physical examination to determine the degree and type of obesity, (3) comorbid conditions, (4) fitness level, and (5) the patient's readiness to adopt lifestyle changes.

The Obesity-Focused History Information from the history should address the following six questions:

- What factors contribute to the patient's obesity?
- How is the obesity affecting the patient's health?
- What is the patient's level of risk from obesity?
- What are the patient's goals and expectations?
- Is the patient motivated to begin a weight management program?
- What kind of help does the patient need?

Although the vast majority of obesity can be attributed to behavioral features that affect diet and physical activity patterns, the history may suggest secondary causes that merit further evaluation. Disorders to consider include polycystic ovarian syndrome, hypothyroidism, Cushing's syndrome, and hypothalamic disease. Drug-induced weight gain should also to be considered. Common causes include antidiabetes agents (insulin, sulfonylureas, thiazolidinediones); steroid hormones; psychotropic agents; mood stabilizers (lithium); antidepressants (tricyclics, monoamine oxidase inhibitors, paraxetine, mirtazapine); and antiepileptic drugs (valproate, gabapentin, carbamazapine). Other medications such as nonsteroidal anti-inflammatory drugs and calcium-channel blockers may cause peripheral edema, but they do not increase body fat.

The patient's current diet and physical activity patterns may reveal factors that contribute to the development of obesity in addition to identifying behaviors to target for treatment. This type of historical information is best obtained by using a questionnaire in combination with an interview.

TABLE 75-1 BODY MASS INDEX (BMI) TABLE

BMI	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Height, inches	Body Weight, pounds																
58	91	96	100	105	110	115	119	124	129	134	138	143	148	153	158	162	167
59	94	99	104	109	114	119	124	128	133	138	143	148	153	158	163	168	173
60	97	102	107	112	118	123	128	133	138	143	148	153	158	163	168	174	179
61	100	106	111	116	122	127	132	137	143	148	153	158	164	169	174	180	185
62	104	109	115	120	126	131	136	142	147	153	158	164	169	175	180	186	191
63	107	113	118	124	130	135	141	146	152	158	163	169	175	180	186	191	197
64	110	116	122	128	134	140	145	151	157	163	169	174	180	186	192	197	204
65	114	120	126	132	138	144	150	156	162	168	174	180	186	192	198	204	210
66	118	124	130	136	142	148	155	161	167	173	179	186	192	198	204	210	216
67	121	127	134	140	146	153	159	166	172	178	185	191	198	204	211	217	223
68	125	131	138	144	151	158	164	171	177	184	190	197	203	210	216	223	230
69	128	135	142	149	155	162	169	176	182	189	196	203	209	216	223	230	236
70	132	139	146	153	160	167	174	181	188	195	202	209	216	222	229	236	243
71	136	143	150	157	165	172	179	186	193	200	208	215	222	229	236	243	250
72	140	147	154	162	169	177	184	191	199	206	213	221	228	235	242	250	258
73	144	151	159	166	174	182	189	197	204	212	219	227	235	242	250	257	265
74	148	155	163	171	179	186	194	202	210	218	225	233	241	249	256	264	272
75	152	160	168	176	184	192	200	208	216	224	232	240	248	256	264	272	279
76	156	164	172	180	189	197	205	213	221	230	238	246	254	263	271	279	287

BMI	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
58	172	177	181	186	191	196	201	205	210	215	220	224	229	234	239	244	248	253	258
59	178	183	188	193	198	203	208	212	217	222	227	232	237	242	247	252	257	262	267
60	184	189	194	199	204	209	215	220	225	230	235	240	245	250	255	261	266	271	276
61	190	195	201	206	211	217	222	227	232	238	243	248	254	259	264	269	275	280	285
62	196	202	207	213	218	224	229	235	240	246	251	256	262	267	273	278	284	289	295
63	203	208	214	220	225	231	237	242	248	254	259	265	270	278	282	287	293	299	304
64	209	215	221	227	232	238	244	250	256	262	267	273	279	285	291	296	302	308	314
65	216	222	228	234	240	246	252	258	264	270	276	282	288	294	300	306	312	318	324
66	223	229	235	241	247	253	260	266	272	278	284	291	297	303	309	315	322	328	334
67	230	236	242	249	255	261	268	274	280	287	293	299	306	312	319	325	331	338	344
68	236	243	249	256	262	269	276	282	289	295	302	308	315	322	328	335	341	348	354
69	243	250	257	263	270	277	284	291	297	304	311	318	324	331	338	345	351	358	365
70	250	257	264	271	278	285	292	299	306	313	320	327	334	341	348	355	362	369	376
71	257	265	272	279	286	293	301	308	315	322	329	338	343	351	358	365	372	379	386
72	265	272	279	287	294	302	309	316	324	331	338	346	353	361	368	375	383	390	397
73	272	280	288	295	302	310	318	325	333	340	348	355	363	371	378	386	393	401	408
74	280	287	295	303	311	319	326	334	342	350	358	365	373	381	389	396	404	412	420
75	287	295	303	311	319	327	335	343	351	359	367	375	383	391	399	407	415	423	431
76	295	304	312	320	328	336	344	353	361	369	377	385	394	402	410	418	426	435	443

BMI and Waist Circumference Three key anthropometric measurements are important to evaluate the degree of obesity—weight, height, and waist circumference. The body mass index (BMI), calculated as weight (kg)/height (m)^2, or as weight (lbs)/height (inches)^2 × 703, is used to classify weight status and risk of disease (Tables 75-1 and 75-2). BMI is used since it provides an estimate of body fat and is related to risk of disease. Lower BMI thresholds for overweight and obesity have been proposed for the Asia-Pacific region since this population appears to be at-risk at lower body weights for glucose and lipid abnormalities.

Excess abdominal fat, assessed by measurement of waist circumference or waist-to-hip ratio, is independently associated with higher risk for diabetes mellitus and cardiovascular disease. Measurement of the waist circumference is a surrogate for visceral adipose tissue and should be performed in the horizontal plane above the iliac crest. Cut points that define higher risk for men and women based on ethnicity have been proposed by the International Diabetes Federation (Table 75-3).

TABLE 75-2 CLASSIFICATION OF WEIGHT STATUS AND RISK OF DISEASE

	BMI (kg/m^2)	Obesity Class	Risk of Disease
Underweight	<18.5		
Healthy weight	18.5–24.9		
Overweight	25.0–29.9		Increased
Obesity	30.0–34.9	I	High
Obesity	35.0–39.9	II	Very high
Extreme Obesity	≥40	III	Extremely high

Source: Adapted from National Institutes of Health, National Heart, Lung, and Blood Institute: *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*. U.S. Department of Health and Human Services, Public Health Service, 1998.

TABLE 75-3 ETHNIC-SPECIFIC VALUES FOR WAIST CIRCUMFERENCE

Ethnic Group	Waist Circumference
Europeans	
Men	>94 cm (37 in)
Women	>80 cm (31.5 in)
South Asians and Chinese	
Men	>90 cm (35 in)
Women	>80 cm (31.5 in)
Japanese	
Men	>85 cm (33.5 in)
Women	>90 cm (35 in)
Ethnic south and central Americans	Use south Asian recommendations until more specific data are available.
Sub-Saharan Africans	Use European data until more specific data are available.
Eastern Mediterranean and Middle East (Arab) populations	Use European data until more specific data are available.

Source: From KGMM Alberti et al for the IDF Epidemiology Task Force Consensus Group: The metabolic syndrome—a new worldwide definition. Lancet 366:1059, 2005.

Physical Fitness Several prospective studies have demonstrated that physical fitness, reported by questionnaire or measured by a maximal treadmill exercise test, is an important predictor of all-cause mortality independent of BMI and body composition. These observations highlight the importance of taking an exercise history during examination as well as emphasizing physical activity as a treatment approach.

Obesity-Associated Comorbid Conditions The evaluation of comorbid conditions should be based on presentation of symptoms, risk factors, and index of suspicion. All patients should have a fasting lipid panel (total, LDL, and HDL cholesterol and triglyceride levels) and blood glucose measured at presentation along with blood pressure determination. Symptoms and diseases that are directly or indirectly related to obesity are listed in Table 75-4. Although individuals vary, the number and severity of organ-specific comorbid conditions usually rise with increasing levels of obesity. Patients at very high absolute risk include the following: established coronary heart disease; presence of other atherosclerotic diseases such as peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease; type 2 diabetes; and sleep apnea.

Assessing the Patient's Readiness to Change An attempt to initiate lifestyle changes when the patient is not ready usually leads to frustration and may hamper future weight-loss efforts. Assessment includes patient motivation and support, stressful life events, psychiatric status, time availability and constraints, and appropriateness of goals and expectations. Readiness can be viewed as the balance of two opposing forces: (1) motivation, or the patient's desire to change; and (2) resistance, or the patient's resistance to change.

A helpful method to begin a readiness assessment is to "anchor" the patient's interest and confidence to change on a numerical scale. Using this technique, the patient is asked to rate his or her level of interest and confidence on a scale from 0 to 10, with 0 being not so important (or confident) and 10 being very important (or confident) to lose weight at this time. This exercise helps to establish readiness to change and also serves as a basis for further dialogue.

TABLE 75-4 OBESITY-RELATED ORGAN SYSTEMS REVIEW

Cardiovascular
- Hypertension
- Congestive heart failure
- Cor pulmonale
- Varicose veins
- Pulmonary embolism
- Coronary artery disease

Endocrine
- Metabolic syndrome
- Type 2 diabetes
- Dyslipidemia
- Polycystic ovarian syndrome

Musculoskeletal
- Hyperuricemia and gout
- Immobility
- Osteoarthritis (knees and hips)
- Low back pain
- Carpal tunnel syndrome

Psychological
- Depression/low self-esteem
- Body image disturbance
- Social stigmatization

Integument
- Striae distensae
- Stasis pigmentation of legs
- Lymphedema
- Cellulitis
- Intertrigo, carbuncles
- Acanthosis nigricans
- Acrochordon (skin tags)
- Hidradenitis suppurativa

Respiratory
- Dyspnea
- Obstructive sleep apnea
- Hypoventilation syndrome
- Pickwickian syndrome
- Asthma

Gastrointestinal
- Gastroesophageal reflux disease
- Nonalcoholic fatty liver disease
- Cholelithiasis
- Hernias
- Colon cancer

Genitourinary
- Urinary stress incontinence
- Obesity-related glomerulopathy
- Hypogonadism (male)
- Breast and uterine cancer
- Pregnancy complications

Neurologic
- Stroke
- Idiopathic intracranial hypertension
- Meralgia paresthetica
- Dementia

Rx OBESITY

THE GOAL OF THERAPY The primary goal of treatment is to improve obesity-related comorbid conditions and reduce the risk of developing future comorbidities. Information obtained from the history, physical examination, and diagnostic tests is used to determine risk and develop a treatment plan **(Fig. 75-1)**. The decision of how aggressively to treat the patient, and which modalities to use, is determined by the patient's risk status, expectations, and available resources. Therapy for obesity always begins with lifestyle management and may include pharmacotherapy or surgery, depending on BMI risk category **(Table 75-5)**. Setting an initial weight-loss goal of 10% over 6 months is a realistic target.

LIFESTYLE MANAGEMENT Obesity care involves attention to three essential elements of lifestyle: dietary habits, physical activity, and behavior modification. Because obesity is fundamentally a disease of energy imbalance, all patients must learn how and when energy is consumed (diet), how and when energy is expended (physical activity), and how to incorporate this information into their daily life (behavior therapy). Lifestyle management has been shown to result in a modest (typically 3–5 kg) weight loss compared to no treatment or usual care.

Diet Therapy The primary focus of diet therapy is to reduce overall caloric consumption. The NHLBI guidelines recommend initiating treatment with a calorie deficit of 500–1000 kcal/d compared to the patient's habitual diet. This reduction is consistent with a goal of losing approximately 1–2 lb per week. This calorie deficit can be accomplished by suggesting substitutions or alternatives to the diet. Examples include choosing smaller portion sizes, eating more fruits and vegetables, consuming more whole-grain cereals, selecting leaner cuts of meat and skimmed dairy products, reducing fried foods and other added fats and oils, and drinking water instead of caloric beverages. It is important that the dietary counseling remains patient-centered and that the goals are practical, realistic, and achievable.

The macronutrient composition of the diet will vary depending on the patient's preference and medical condition. The 2005 U.S. Department of Agriculture Dietary Guidelines for Americans (Chap. 70), which focus on health promotion and risk reduction, can be applied to treatment of the overweight or obese patient. The recommendations include maintaining a diet rich in whole grains, fruits, vegetables, and dietary fiber; consuming two servings (8 oz) of fish high in omega 3 fatty acids per week; decreasing sodium to <2300 mg/d; consuming 3 cups of milk (or equivalent low-fat or fat-free dairy products) per day; limiting cholesterol to <300 mg/d; and keeping total fat between 20 and 35% of daily calories and saturated fats to <10% of daily calories. Application of these guidelines to specific calorie goals can be found on the website *www.mypyramid.gov*. The revised Dietary Reference Intakes for Macronutrients released by the Institute of Medicine recommends 45–65% of calories from carbohydrates, 20–35% from fat, and 10–35% from protein. The guidelines also recommend daily fiber intake of 38 g (men) and 25 g (women) for persons over 50 years of age and 30 g (men) and 21 g (women) for those under 50.

Since portion control is one of the most difficult strategies for patients to manage, the use of pre-prepared products, such as meal replacements, is a simple and convenient suggestion. Examples include frozen entrees, canned beverages and bars. Use of meal replacements in the diet has been shown to result in a 7–8% weight loss.

A current area of controversy is the use of low-carbohydrate, high-protein diets for weight loss. These diets are based on the concept that carbohydrates are the primary cause of obesity and lead to insulin resistance. Most low-carbohydrate diets (e.g., South Beach, Zone, and Sugar Busters!) recommend a carbohydrate level of approximately 40–46% of energy. The Atkins diet contains 5–15% carbohydrate, depending on the phase of the diet. Several randomized, controlled trials of these low-carbohydrate diets have demonstrated greater weight loss at 6 months with improvement in coronary heart disease risk factors, including an increase in HDL cholesterol and a decrease in triglyceride levels. Weight loss between groups did not remain statistically significant at 1 year; however, low-carbohydrate diets appear to be at least as effective as low-fat diets in inducing weight loss for up to 1 year.

Another dietary approach to consider is the concept of energy density, which refers to the number of calories (energy) a food contains per unit of weight. People tend to ingest a constant volume of food, regardless of caloric or macronutrient content. Adding water or fiber to a food decreases its energy density by increasing weight without affecting caloric content. Examples of foods with low-energy density include soups, fruits, vegetables, oatmeal, and lean meats. Dry foods and high-fat foods such as pret-

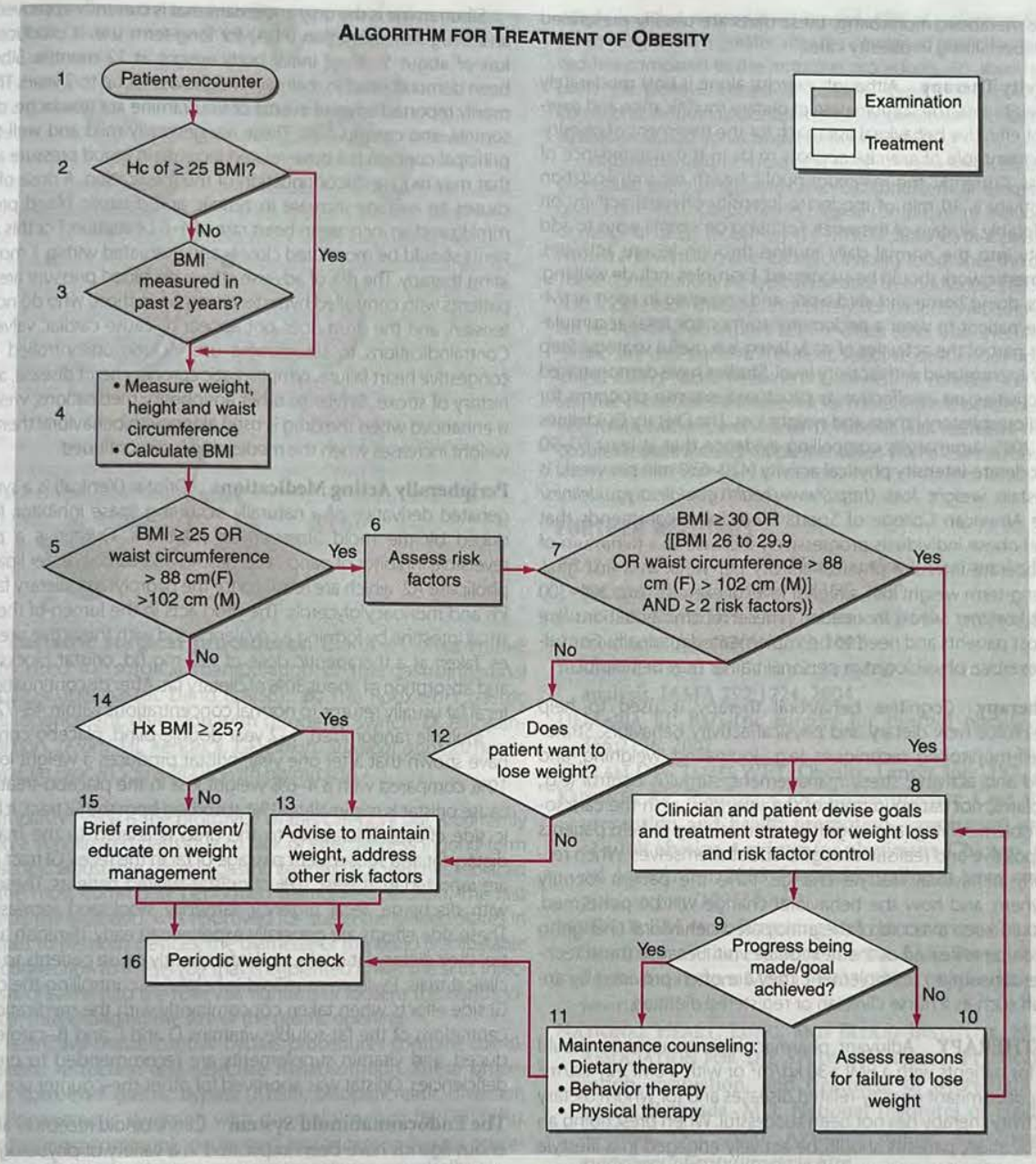


FIGURE 75-1 Treatment algorithm. This algorithm applies only to the assessment for overweight and obesity and subsequent decisions on that assessment. It does not reflect any initial overall assessment for other conditions that the physician may wish to perform. Ht, height; Hx, history; Wt, weight. *(From National, Heart, Lung, and Blood Institute: Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: The evidence report. Washington, DC, US Department of Health and Human Services, 1998.)*

zels, cheese, egg yolks, potato chips, and red meat have a high-energy density. Diets containing low-energy dense foods have been shown to control hunger and result in decreased caloric intake and weight loss.

Occasionally, very-low-calorie diets (VLCDs) are prescribed as a form of aggressive dietary therapy. The primary purpose of a VLCD is to promote a rapid and significant (13–23 kg) short-term weight loss over a 3–6 month period. These propriety formulas typically supply ≤800 kcal, 50–80 g protein, and 100% of the recommended daily intake for vitamins and minerals. According to a review by the National Task Force on the Prevention and Treatment of Obesity, indications for initiating a VLCD include well-motivated individuals who are moderately to severely obese (BMI >30), have failed at more conservative approaches to weight loss, and have a medical condition that would be immediately improved with rapid weight loss. These conditions include poorly controlled type 2 diabetes, hypertriglyceridemia, obstructive sleep apnea, and symptomatic peripheral edema. The risk for gallstone formation increases exponentially at rates of weight loss >1.5 kg/week (3.3 lb/week). Prophylaxis against gallstone formation with ursodeoxycholic acid, 600 mg/d, is effective in reducing this risk. Because of the

TABLE 75-5 A GUIDE TO SELECTING TREATMENT

	BMI Category				
Treatment	**25–26.9**	**27–29.9**	**30–35**	**35–39.9**	**≥40**
Diet, exercise, behavior therapy	With comorbidities	With comorbidities	+	+	+
Pharmacotherapy		With comorbidities	+	+	+
Surgery				With comorbidities	+

Source: From National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity (2000).

need for close metabolic monitoring, these diets are usually prescribed by physicians specializing in obesity care.

Physical Activity Therapy Although exercise alone is only moderately effective for weight loss, the combination of dietary modification and exercise is the most effective behavioral approach for the treatment of obesity. The most important role of exercise appears to be in the maintenance of the weight loss. Currently, the *minimum* public health recommendation for physical activity is 30 min of moderate intensity physical activity on most, and preferably all, days of the week. Focusing on simple ways to add physical activity into the normal daily routine through leisure activities, travel, and domestic work should be suggested. Examples include walking, using the stairs, doing home and yard work, and engaging in sport activities. Asking the patient to wear a pedometer to monitor total accumulation of steps as part of the activities of daily living is a useful strategy. Step counts are highly correlated with activity level. Studies have demonstrated that lifestyle activities are as effective as structured exercise programs for improving cardiorespiratory fitness and weight loss. The Dietary Guidelines for Americans 2005 summarizes compelling evidence that at least 60–90 min of daily moderate-intensity physical activity (420–630 min per week) is needed to sustain weight loss (*http://www.health.gov/dietaryguidelines/dga2005/*). The American College of Sports Medicine recommends that overweight and obese individuals progressively increase to a minimum of 150 min of moderate intensity physical activity per week as a first goal. However, for long-term weight loss, a higher level of exercise (e.g., 200–300 min or ≥2000 kcal per week) is needed. These recommendations are daunting to most patients and need to be implemented gradually. Consultation with an exercise physiologist or personal trainer may be helpful.

Behavioral Therapy Cognitive behavioral therapy is used to help change and reinforce new dietary and physical activity behaviors. Strategies include self-monitoring techniques (e.g., journaling, weighing, and measuring food and activity); stress management; stimulus control (e.g., using smaller plates, not eating in front of the television or in the car); social support; problem solving; and cognitive restructuring to help patients develop more positive and realistic thoughts about themselves. When recommending any behavioral lifestyle change, have the patient identify what, when, where, and how the behavioral change will be performed. The patient should keep a record of the anticipated behavioral change so that progress can be reviewed at the next office visit. Because these techniques are time-consuming to implement, they are often provided by ancillary office staff such as a nurse clinician or registered dietitian.

PHARMACOTHERAPY Adjuvant pharmacologic treatments should be considered for patients with a BMI >30 kg/m^2 or with a BMI >27 kg/m^2 who also have concomitant obesity-related diseases and for whom dietary and physical activity therapy has not been successful. When prescribing an antiobesity medication, patients should be actively engaged in a lifestyle program that provides the strategies and skills needed to effectively use the drug since this support increases total weight loss.

There are several potential targets of pharmacologic therapy for obesity. The most thoroughly explored treatment is suppression of appetite via centrally active medications that alter monoamine neurotransmitters. A second strategy is to reduce the absorption of selective macronutrients from the gastrointestinal (GI) tract, such as fat. These two mechanisms form the basis for all currently prescribed antiobesity agents. A third target, selective blocking of the endocannabinoid system, has recently been identified.

Centrally Acting Anorexiant Medications Appetite-suppressing drugs, or anorexiants, affect satiety—the absence of hunger after eating—and hunger—a biologic sensation that initiates eating. By increasing satiety and decreasing hunger, these agents help patients reduce caloric intake without a sense of deprivation. The target site for the actions of anorexiants is the ventromedial and lateral hypothalamic regions in the central nervous system (Chap. 74). Their biological effect on appetite regulation is produced by augmenting the neurotransmission of three monoamines: norepinephrine; serotonin [5-hydroxytryptamine (5-HT)]; and, to a lesser degree, dopamine. The classic sympathomimetic adrenergic agents (benzphetamine, phendimetrazine, diethylpropion, mazindol, and phentermine) function by stimulating norepinephrine release or by blocking its reuptake. In contrast, sibutramine (Meridia) functions as a serotonin and norepinephrine reuptake inhibitor. Unlike other previously used anorexiants, sibutramine is not pharmacologically related to amphetamine and has no addictive potential.

Sibutramine is the only anorexiant that is currently approved by the Food and Drug Administration (FDA) for long-term use. It produces an average loss of about 5–9% of initial body weight at 12 months. Sibutramine has been demonstrated to maintain weight loss for up to 2 years. The most commonly reported adverse events of sibutramine are headache, dry mouth, insomnia, and constipation. These are generally mild and well-tolerated. The principal concern is a dose-related increase in blood pressure and heart rate that may require discontinuation of the medication. A dose of 10–15 mg/d causes an average increase in systolic and diastolic blood pressure of 2–4 mmHg and an increase in heart rate of 4–6 beats/min. For this reason, all patients should be monitored closely and evaluated within 1 month after initiating therapy. The risk of adverse effects on blood pressure are no greater in patients with controlled hypertension than in those who do not have hypertension, and the drug does not appear to cause cardiac valve dysfunction. Contraindications to sibutramine use include uncontrolled hypertension, congestive heart failure, symptomatic coronary heart disease, arrhythmias, or history of stroke. Similar to other antiobesity medications, weight reduction is enhanced when the drug is used along with behavioral therapy, and body weight increases when the medication is discontinued.

Peripherally Acting Medications Orlistat (Xenical) is a synthetic hydrogenated derivative of a naturally occurring lipase inhibitor, lipostatin, produced by the mold *Streptomyces toxytricini*. Orlistat is a potent, slowly reversible inhibitor of pancreatic, gastric, and carboxylester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat into fatty acids and monoacylglycerols. The drug acts in the lumen of the stomach and small intestine by forming a covalent bond with the active site of these lipases. Taken at a therapeutic dose of 120 mg tid, orlistat blocks the digestion and absorption of about 30% of dietary fat. After discontinuation of the drug, fecal fat usually returns to normal concentrations within 48–72 h.

Multiple randomized, 1–2 year double-blind, placebo-controlled studies have shown that after one year, orlistat produces a weight loss of about 9–10%, compared with a 4–6% weight loss in the placebo-treated groups. Because orlistat is minimally (<1%) absorbed from the GI tract, it has no systemic side effects. Tolerability to the drug is related to the malabsorption of dietary fat and subsequent passage of fat in the feces. GI tract adverse effects are reported in at least 10% of orlistat-treated patients. These include flatus with discharge, fecal urgency, fatty/oily stool, and increased defecation. These side effects are generally experienced early, diminish as patients control their dietary fat intake, and infrequently cause patients to withdraw from clinical trials. Psyllium mucilloid is helpful in controlling the orlistat-induced GI side effects when taken concomitantly with the medication. Serum concentrations of the fat-soluble vitamins D and E and β–carotene may be reduced, and vitamin supplements are recommended to prevent potential deficiencies. Orlistat was approved for other-the-counter use in 2007.

The Endocannabinoid System Cannabinoid receptors and their endogenous ligands have been implicated in a variety of physiologic functions, including feeding, modulation of pain, emotional behavior, and peripheral lipid metabolism. Cannabis and its main ingredient, Δ^9-tetrahydrocannabinol (THC), is an exogenous cannabinoid compound. Two endocannabinoids have been identified, anandamide and 2-arachidonyl glyceride. Two cannabinoid receptors have been identified: CB_1 (abundant in the brain) and CB_2 (present in immune cells). The brain endocannabinoid system is thought to control food intake through reinforcing motivation to find and consume foods with high incentive value and to regulate actions of other mediators of appetite. The first selective cannabinoid CB_1 receptor antagonist, rimonabant, was discovered in 1994. The medication antagonizes the orexigenic effect of THC and suppresses appetite when given alone in animal models. Several large prospective, randomized controlled trials have demonstrated the effectiveness of rimonabant as a weight-loss agent. Taken as a 20 mg dose, subjects lost an average of 6.5 kg (14.32 lb) compared to 1.5 kg (3.3 lb) for placebo at 1 year. Concomitant improvements were seen in waist circumference and cardiovascular risk factors. The most common reported side effects include depression, anxiety, and nausea. FDA approval of Rimonabant is still pending.

SURGERY Bariatric surgery can be considered for patients with severe obesity (BMI ≥40 kg/m^2) or those with moderate obesity (BMI ≥35 kg/m^2) associated with a serious medical condition. Surgical weight loss functions by reducing caloric intake and, depending on the procedure, macronutrient absorption.

Weight-loss surgeries fall into one of two categories: restrictive and restrictive-malabsorptive **(Fig. 75-2)**. Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. The vertical

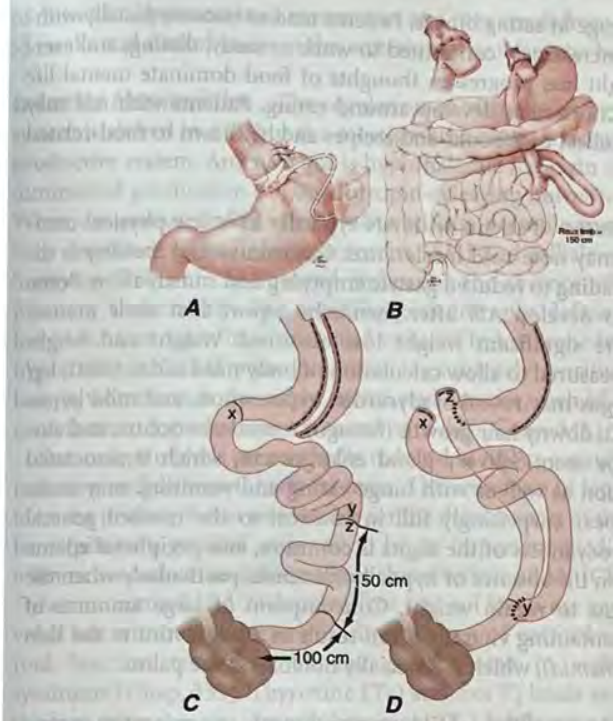


FIGURE 75-2 Bariatric surgical procedures. Examples of operative interventions used for surgical manipulation of the gastrointestinal tract. ***A.*** Laparoscopic gastric band (LAGB). ***B.*** The Roux-en-Y gastric bypass. ***C.*** Biliopancreatic diversion with duodenal switch. ***D.*** Biliopancreatic diversion. *(From ML Kendrick, GF Dakin. Surgical approaches to obesity. Mayo Clin Proc 815:518, 2006; with permission.)*

banded gastroplasty (VBG) is the prototype of this category but is currently performed on a very limited basis due to lack of effectiveness in long-term trials. Laparoscopic adjustable silicone gastric banding (LASGB) has replaced the VBG as the most commonly performed restrictive operation. The first banding device, the lap-band, was approved for use in the United States in 2001. In contrast to previous devices, the diameter of this band is adjustable by way of its connection to a reservoir that is implanted under the skin. Injection or removal of saline into the reservoir tightens or loosens the band's internal diameter, thus changing the size of the gastric opening.

The three restrictive-malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption. These procedures include Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion (BPD), and biliopancreatic diversion with duodenal switch (BPDDS) (Fig. 75-2). RYGB is the most commonly performed and accepted bypass procedure. It may be performed with an open incision or laparoscopically.

Although no recent randomized controlled trials compare weight loss after surgical and nonsurgical interventions, data from meta-analyses and large databases, primarily obtained from observational studies, suggest that bariatric surgery is the most effective weight-loss therapy for those with clinically severe obesity. These procedures generally produce a 30–35% average total body weight loss that is maintained in nearly 60% of patients at 5 years. In general, mean weight loss is greater after the combined restrictive-malabsorptive procedures compared to the restrictive procedures. An abundance of data supports the positive impact of bariatric surgery on obesity-related morbid conditions, including diabetes mellitus, hypertension, obstructive sleep apnea, dyslipidemia, and nonalcoholic fatty liver disease.

Surgical mortality from bariatric surgery is generally <1% but varies with the procedure, patient's age and comorbid conditions, and experience of the surgical team. The most common surgical complications include stomal stenosis or marginal ulcers (occurring in 5–15% of patients) that present as prolonged nausea and vomiting after eating or inability to advance the diet to solid foods. These complications are typically treated by endoscopic balloon dilatation and acid suppression therapy, respectively. For patients who undergo LASGB, there are no intestinal absorptive abnormalities other than mechanical reduction in gastric size and outflow. Therefore, selective deficiencies occur uncommonly unless eating habits become unbalanced. In contrast, the restrictive-malabsorptive procedures increase risk for micronutrient deficiencies of vitamin B_{12}, iron, folate, calcium, and vitamin D. Patients with restrictive-malabsorptive procedures require lifelong supplementation with these micronutrients.

FURTHER READINGS

BRAY GA, GREENWAY FL: Pharmacologic treatment of the overweight patient. Pharmacol Rev 59:151, 2007

BRAY GA, RYAN DH: Drug treatment of the overweight patient. Gastroenterology 132(6):2239, 2007

BUCHWALD H et al: Bariatric surgery: A systematic review and meta-analysis. JAMA 292:1724, 2004

DEMARIA EJ: Bariatric surgery for morbid obesity. N Engl J Med 356:2176, 2007

HASLAM DW, JAMES WPT: Obesity. Lancet 366:1197, 2005

KUSHNER RF: Roadmaps for clinical practice: Case studies in disease prevention and health promotion—assessment and management of adult obesity: A primer for physicians. Chicago, American Medical Association, 2003. (Available online at *www.ama-assn.org/ama/pub/category/10931.html*)

MCTIGUE KM et al: Screening and interventions for obesity in adults: Summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 139:933, 2003. (Appendix tables available at *www.annals.org*)

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, NORTH AMERICAN ASSOCIATION FOR THE STUDY OF OBESITY: Practical guide: Identification, evaluation, and treatment of overweight and obesity in adults. Bethesda, MD, National Institutes of Health pub number 00-4084, Oct. 2000. Available online: *http://www.nhlbi.nih.gov/guidelines/obesity/practgde.htm*

PADWAL R et al: Long-term pharmacotherapy for overweight and obesity: A systematic review and meta-analysis of randomized controlled trials. Int J Obesity 27:1437, 2003

WADDEN TA et al: Lifestyle modification for the management of obesity. Gastroenterology 132(6):2226, 2007

76 Eating Disorders

B. Timothy Walsh

Anorexia nervosa and bulimia nervosa are characterized by severe disturbances of eating behavior. The salient feature of *anorexia nervosa* (AN) is a refusal to maintain a minimally normal body weight. *Bulimia nervosa* (BN) is characterized by recurrent episodes of binge eating followed by abnormal compensatory behaviors, such as self-induced vomiting. AN and BN are distinct clinical syndromes but share certain features in common. Both disorders occur primarily among previously healthy young women who become overly concerned with body shape and weight. Many patients with BN have past histories of anorexia nervosa, and many patients with AN engage in binge eating and purging behavior. In the current diagnostic system, the critical distinction between AN and BN depends on body weight: patients with AN are, by definition, significantly underweight, whereas patients with BN have body weights in the normal range or above.

Binge eating disorder (BED) is a more recently described syndrome characterized by repeated episodes of binge eating, similar to those of BN, in the absence of inappropriate compensatory behavior. Patients with BED are typically middle-aged men or women with significant obesity. They have an increased frequency of anxiety and depression compared to similarly obese patients without BED. It is not established that patients with BED are at increased risk for medical complications or that they require specific treatment interventions.

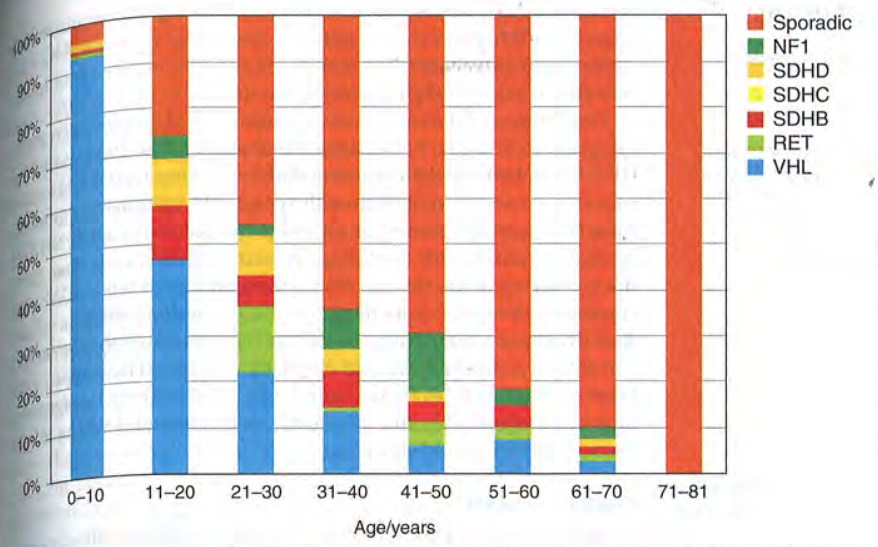


FIGURE 337-6 Mutation distribution in the *RET*, *VHL*, *NF1*, *SDHB*, *SDHC*, and *SDHD* genes. The bars depict the frequency of sporadic or various inherited forms of pheochromocytoma in different age groups. The inherited disorders are much more common among younger individuals presenting with pheochromocytoma. *(Data from the Freiburg International Pheochromocytoma and Paraganglioma Registry.)*

Once the underlying syndrome is diagnosed, the benefit of genetic testing can be extended to relatives. For this purpose, it is necessary to identify the germ-line mutation in the proband and, after genetic counseling, perform DNA sequence analyses of the responsible gene in relatives to determine if they are affected (Chap. 64). Other family members may benefit from biochemical screening for tumors in individuals who carry a germ-line mutation.

FURTHER READINGS

BAUSCH B et al: Clinical and genetic characteristics of patients with neurofibromatosis type 1 and pheochromocytoma. N Engl J Med 354:2729, 2006

——— et al: Germline NF1 mutational spectra and loss-of-heterozygosity analyses in patients with pheochromocytoma and neurofibromatosis type 1. J Clin Endocrinol Metab 92:2784, 2007

LENDERS JW et al: Phaeochromocytoma. Lancet 366:665, 2005

NEUMANN HP et al: Distinct clinical features of paraganglioma syndromes associated with *SDHB* and *SDHD* gene mutations. JAMA 292:943, 2004

——— et al: Evidence of MEN-2 in the original description of classic pheochromocytoma. N Engl J Med 357:1311, 2007

——— et al: Germline mutations in nonsyndromic pheochromocytoma. N Engl J Med 346:1459, 2002

SCHOLZ T et al: Clinical review: Current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab 92:1217, 2007

WALZ MK et al: Laparoscopic and retroperitoneoscopic treatment of pheochromocytomas and retroperitoneal paragangliomas: Results of 161 tumors in 126 patients. World J Surg 30:899, 2006

338 Diabetes Mellitus

Alvin C. Powers

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

CLASSIFICATION

DM is classified on the basis of the pathogenic process that leads to hyperglycemia, as opposed to earlier criteria such as age of onset or type of therapy (Fig. 338-1). The two broad categories of DM are designated type 1 and type 2 (Table 338-1). Both types of diabetes are preceded by a phase of abnormal glucose homeostasis as the pathogenic processes progresses. Type 1 diabetes is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 DM and have important potential

Type of Diabetes	Normal glucose tolerance	Hyperglycemia: Pre-diabetes: Impaired fasting glucose or impaired glucose tolerance	Hyperglycemia: Diabetes Mellitus: Not insulin requiring	Hyperglycemia: Diabetes Mellitus: Insulin required for control	Hyperglycemia: Diabetes Mellitus: Insulin required for survival
Type 1					
Type 2					
Other specific types					
Gestational Diabetes					
Time (years)					
FPG	<5.6 mmol/L (100 mg/dL)	5.6–6.9 mmol/L (100–125 mg/dL)	≥7.0 mmol/L (126 mg/dL)		
2-h PG	<7.8 mmol/L (140 mg/dL)	7.8–11.1 mmol/L (140–199 mg/dL)	≥11.1 mmol/L (200 mg/dL)		

FIGURE 338-1 Spectrum of glucose homeostasis and diabetes mellitus (DM). The spectrum from normal glucose tolerance to diabetes in type 1 DM, type 2 DM, other specific types of diabetes, and gestational DM is shown from left to right. In most types of DM, the individual traverses from normal glucose tolerance to impaired glucose tolerance to overt diabetes. Arrows indicate that changes in glucose tolerance may be bi-directional in some types of diabetes. For example, individuals with type 2 DM may return to the impaired glucose tolerance category with weight loss; in gestational DM diabetes may revert to impaired glucose tolerance or even normal glucose tolerance after delivery. The fasting plasma glucose (FPG) and 2-h plasma glucose (PG), after a glucose challenge for the different categories of glucose tolerance, are shown at the lower part of the figure. These values do not apply to the diagnosis of gestational DM. Some types of DM may or may not require insulin for survival, hence the dotted line. (Conventional units are used in the figure.) *(Adapted from the American Diabetes Association, 2007.)*

TABLE 338-1 ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

I. Type 1 diabetes (β-cell destruction, usually leading to absolute insulin deficiency)
  A. Immune-mediated
  B. Idiopathic
II. Type 2 diabetes (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
III. Other specific types of diabetes
  A. Genetic defects of β cell function characterized by mutations in:
    1. Hepatocyte nuclear transcription factor (HNF) 4α (MODY 1)
    2. Glucokinase (MODY 2)
    3. HNF-1α (MODY 3)
    4. Insulin promoter factor-1 (IPF-1; MODY 4)
    5. HNF-1β (MODY 5)
    6. NeuroD1 (MODY 6)
    7. Mitochondrial DNA
    8. Subunits of ATP-sensitive potassium channel
    9. Proinsulin or insulin conversion
  B. Genetic defects in insulin action
    1. Type A insulin resistance
    2. Leprechaunism
    3. Rabson-Mendenhall syndrome
    4. Lipodystrophy syndromes
  C. Diseases of the exocrine pancreas—pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, fibrocalculous pancreatopathy, mutations in carboxyl ester lipase
  D. Endocrinopathies—acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, hyperthyroidism, somatostatinoma, aldosteronoma
  E. Drug- or chemical-induced—Vacor, pentamidine, nicotinic acid, glucocorticoids, thyroid hormone, diazoxide, β-adrenergic agonists, thiazides, phenytoin, α-interferon, protease inhibitors, clozapine
  F. Infections—congenital rubella, cytomegalovirus, coxsackie
  G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies
  H. Other genetic syndromes sometimes associated with diabetes—Down's syndrome, Klinefelter's syndrome, Turner's syndrome, Wolfram's syndrome, Friedreich's ataxia, Huntington's chorea, Laurence-Moon-Biedl syndrome, myotonic dystrophy, porphyria, Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Note: MODY, maturity onset of diabetes of the young.
Source: Adapted from American Diabetes Association, 2007

therapeutic implications now that pharmacologic agents are available to target specific metabolic derangements. Type 2 DM is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT).

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

OTHER TYPES OF DM

Other etiologies for DM include specific genetic defects in insulin secretion or action, metabolic abnormalities that impair insulin secretion, mitochondrial abnormalities, and a host of conditions that impair glucose tolerance (Table 338-1). *Maturity onset diabetes of the young* (MODY) is a subtype of DM characterized by autosomal dominant inheritance, early onset of hyperglycemia (usually <25 years), and impairment in insulin secretion (discussed below). Mutations in the insulin receptor cause a group of rare disorders characterized by severe insulin resistance.

DM can result from pancreatic exocrine disease when the majority of pancreatic islets are destroyed. Hormones that antagonize insulin action can also lead to DM. Thus, DM is often a feature of endocrinopathies such as acromegaly and Cushing's disease. Viral infections have been implicated in pancreatic islet destruction but are an extremely rare cause of DM. A form of acute onset of type 1 diabetes, termed *fulminant diabetes*, has been noted in Japan and may be related to viral infection of islets.

GESTATIONAL DIABETES MELLITUS (GDM)

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

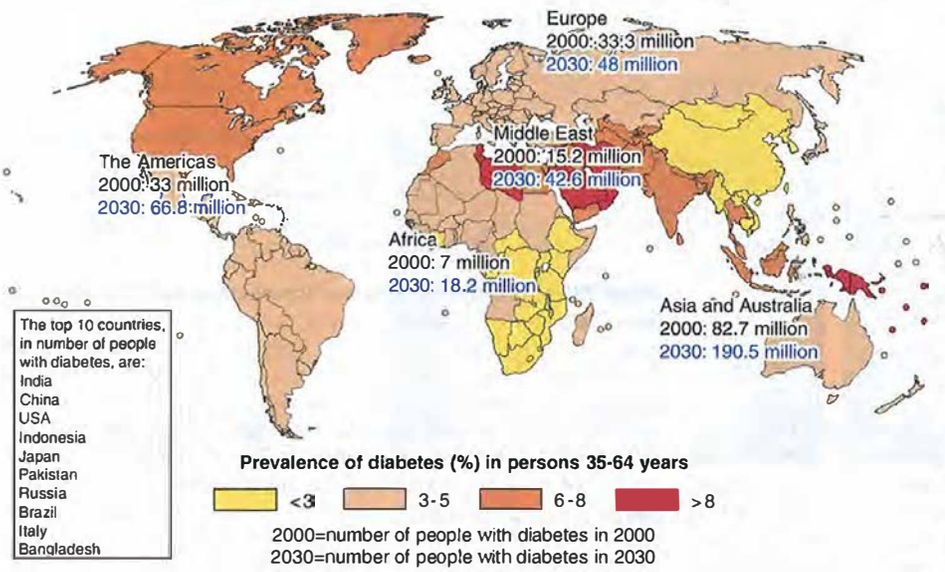


FIGURE 338-2 Worldwide prevalence of diabetes mellitus. The prevalence of diabetes in 2000 and the projected prevalence in 2030 are shown by geographical region. *(Used with permission from Diabetes Action Now: An Initiative of the World Health Organization and the International Diabetes Federation, 2004, as adapted from S Wild et al: Diabetes Care 27:1047, 2004.)*

EPIDEMIOLOGY

The worldwide prevalence of DM has risen dramatically over the past two decades, from an estimated 30 million cases in 1985 to 177 million in 2000. Based on current trends, >360 million individuals will have diabetes by the year 2030 (Fig. 338-2). Although the prevalence of both type 1 and type 2 DM is increasing worldwide, the prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized. This is true in most countries, and 6 of the top 10 countries with the highest rates are in Asia. In the United States, the Centers for Disease Control and Prevention (CDC) estimated that 20.8 million persons, or 7% of the population, had diabetes in 2005 (~30% of individuals with diabetes were undiagnosed). Approximately 1.5

million individuals (>20 years) were newly diagnosed with diabetes in 2005. DM increases with aging. In 2005, the prevalence of DM in the United States was estimated to be 0.22% in those <20 years and 9.6% in those >20 years. In individuals >60 years, the prevalence of DM was 20.9%. The prevalence is similar in men and women throughout most age ranges (10.5% and 8.8% in individuals >20 years) but is slightly greater in men >60 years. Worldwide estimates project that in 2030 the greatest number of individuals with diabetes will be 45–64 years of age.

There is considerable geographic variation in the incidence of both type 1 and type 2 DM. Scandinavia has the highest incidence of type 1 DM (e.g., in Finland, the incidence is 35/100,000 per year). The Pacific Rim has a much lower rate (in Japan and China, the incidence is 1–3/100,000 per year) of type 1 DM; Northern Europe and the United States have an intermediate rate (8–17/100,000 per year). Much of the increased risk of type 1 DM is believed to reflect the frequency of high-risk HLA alleles among ethnic groups in different geographic locations. The prevalence of type 2 DM and its harbinger, IGT, is highest in certain Pacific islands, intermediate in countries such as India and the United States, and relatively low in Russia. This variability is likely due to genetic, behavioral, and environmental factors. DM prevalence also varies among different ethnic populations within a given country. In 2005, the CDC estimated that the prevalence of DM in the United States (age > 20 years) was 13.3% in African Americans, 9.5% in Latinos, 15.1% in Native Americans (American Indians and Alaska natives), and 8.7% in non-Hispanic whites. Individuals belonging to Asian-American or Pacific-Islander ethnic groups in Hawaii are twice as likely to have diabetes compared to non-Hispanic whites. The onset of type 2 DM occurs, on average, at an earlier age in ethnic groups other than non-Hispanic whites.

Diabetes is a major cause of mortality, but several studies indicate that diabetes is likely underreported as a cause of death. In the United States, diabetes was listed as the sixth-leading cause of death in 2002; a recent estimate suggested that diabetes was the fifth leading cause of death worldwide and was responsible for almost 3 million deaths annually (1.7–5.2% of deaths worldwide).

DIAGNOSIS

The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM (Table 338-2) based on the following premises: (1) the spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load (OGTT—oral glucose tolerance test) varies among normal individuals, and (2) DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations from a population-based mean. For example, the prevalence of retinopathy in Native Americans (Pima Indian population) begins to increase at a FPG > 6.4 mmol/L (116 mg/dL) (Fig. 338-3).

Glucose tolerance is classified into three categories based on the FPG (Fig. 338-1): (1) FPG < 5.6 mmol/L (100 mg/dL) is considered normal; (2) FPG = 5.6–6.9 mmol/L (100–125 mg/dL) is defined as IFG; and (3) FPG ≥7.0 mmol/L (126 mg/dL) warrants the diagnosis of DM. Based on the OGTT, IGT is defined as plasma glucose levels between 7.8 and 11.1 mmol/L (140 and 199 mg/dL) and diabetes is defined as a glucose > 11.1 mmol/L (200 mg/dL) 2 h after a 75-g oral glucose load (Table 338-2). Some individuals have both IFG and IGT. Individuals with IFG and/or IGT, recently designated *pre-diabetes* by the American Diabetes Association (ADA), are at substantial risk for developing type 2 DM (25–40% risk over the next 5 years) and have an increased risk of cardiovascular disease.

TABLE 338-2 CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

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

[a] Random is defined as without regard to time since the last meal.
[b] Fasting is defined as no caloric intake for at least 8 h.
[c] The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water; not recommended for routine clinical use.
Note: In the absence of unequivocal hyperglycemia and acute metabolic decompensation, these criteria should be confirmed by repeat testing on a different day.
Source: Adapted from American Diabetes Association, 2007.

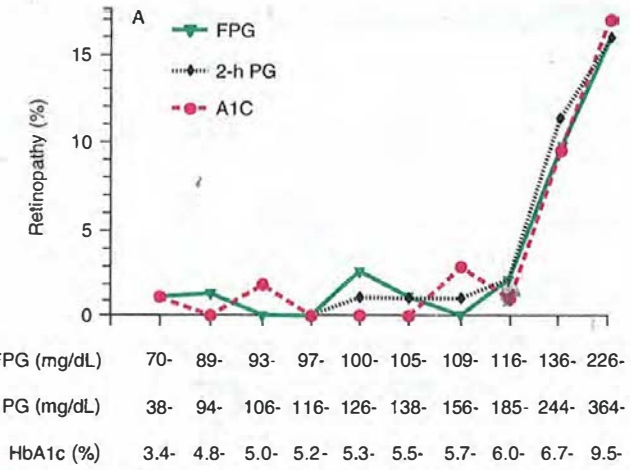


FIGURE 338-3 Relationship of diabetes-specific complication and glucose tolerance. This figure shows the incidence of retinopathy in Pima Indians as a function of the fasting plasma glucose (FPG), the 2-h plasma glucose after a 75-g oral glucose challenge (2-h PG), or glycated hemoglobin (A1C). Note that the incidence of retinopathy greatly increases at a fasting plasma glucose >116 mg/dL, or a 2-h plasma glucose of 185 mg/dL, or a A1C >6.0%. (Blood glucose values are shown in mg/dL; to convert to mmol/L, divide value by 18.) *(Copyright 2002, American Diabetes Association. From Diabetes Care 25(Suppl 1): S5–S20, 2002.)*

The current criteria for the diagnosis of DM emphasize that the FPG is the most reliable and convenient test for identifying DM in asymptomatic individuals. A random plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is sufficient for the diagnosis of DM (Table 338-2). Oral glucose tolerance testing, although still a valid means for diagnosing DM, is not recommended as part of routine care.

Some investigators have advocated the hemoglobin A1C (A1C) as a diagnostic test for DM. Though there is a strong correlation between elevations in the plasma glucose and the A1C (discussed below), the relationship between the FPG and the A1C in individuals with normal glucose tolerance or mild glucose intolerance is less clear, and thus the use of the A1C is not currently recommended to diagnose diabetes.

The diagnosis of DM has profound implications for an individual from both a medical and financial standpoint. Thus, these diagnostic criteria must be satisfied before assigning the diagnosis of DM. Abnormalities on screening tests for diabetes should be repeated before making a definitive diagnosis of DM, unless acute metabolic derangements or a markedly elevated plasma glucose are present (Table 338-2). The revised criteria also allow for the diagnosis of DM to be withdrawn in situations where the FPG reverts to normal.

SCREENING

Widespread use of the FPG as a screening test for type 2 DM is recommended because: (1) a large number of individuals who meet the current criteria for DM are asymptomatic and unaware that they have the disorder, (2) epidemiologic studies suggest that type 2 DM may be present for up to a decade before diagnosis, (3) as many as 50% of individuals with type 2 DM have one or more diabetes-specific complications at the time of their diagnosis, and (4) treatment of type 2 DM may favorably alter the natural history of DM. The ADA recommends screening all individuals >45 years every 3 years and screening individuals at an earlier age if they are overweight [body mass index (BMI) > 25 km/m^2] and have one additional risk factor for diabetes

TABLE 338-3 RISK FACTORS FOR TYPE 2 DIABETES MELLITUS

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

Note: BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein.
Source: Adapted from American Diabetes Association, 2007.

(Table 338-3). In contrast to type 2 DM, a long asymptomatic period of hyperglycemia is rare prior to the diagnosis of type 1 DM. A number of immunologic markers for type 1 DM are becoming available (discussed below), but their routine use is discouraged pending the identification of clinically beneficial interventions for individuals at high risk for developing type 1 DM.

INSULIN BIOSYNTHESIS, SECRETION, AND ACTION

BIOSYNTHESIS

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the amino-terminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor. Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells. Because the C peptide is cleared more slowly than insulin, it is a useful marker of insulin secretion and allows discrimination of endogenous and exogenous sources of insulin in the evaluation of hypoglycemia (Chaps. 339 and 344). Pancreatic beta cells cosecrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino-acid peptide, along with insulin. The role of IAPP in normal physiology is unclear, but it is the major component of the amyloid fibrils found in the islets of patients with type 2 diabetes, and an analogue is sometimes used in treating both type 1 and type 2 DM. Human insulin is now produced by recombinant DNA technology; structural alterations at one or more residues are useful for modifying its physical and pharmacologic characteristics (see below).

SECRETION

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels > 3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by the GLUT2 glucose transporter (Fig. 338-4). Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates ATP, which inhibits the activity of an ATP-sensitive K^+ channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (e.g., sulfonylureas, meglitinides); the other is an inwardly rectifying K^+ channel protein (Kir6.2). Inhibition of this K^+ channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 min, superimposed upon greater amplitude oscillations of about 80–150 min. Incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion. Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level. Incretin analogues, such as exena-tide, are being used to enhance endogenous insulin secretion (see below).

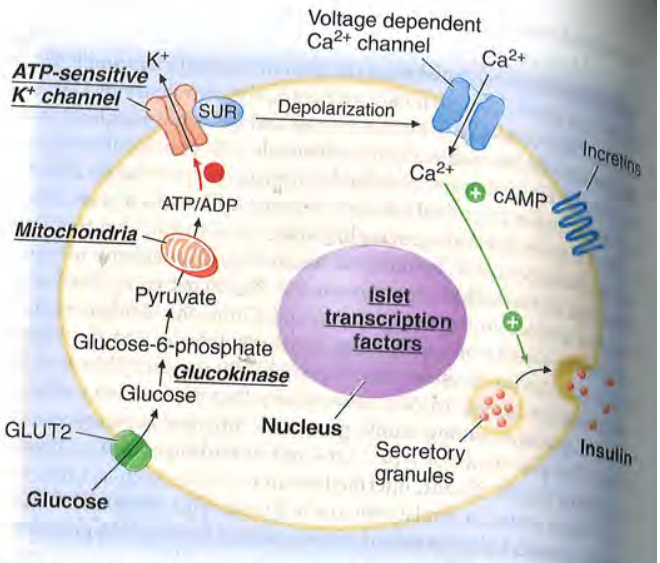


FIGURE 338-4 Diabetes and abnormalities in glucose-stimulated insulin secretion. Glucose and other nutrients regulate insulin secretion by the pancreatic beta cell. Glucose is transported by the GLUT2 glucose transporter; subsequent glucose metabolism by the beta cell alters ion channel activity, leading to insulin secretion. The SUR receptor is the binding site for drugs that act as insulin secretagogues. Mutations in the events or proteins underlined are a cause of maturity onset diabetes of the young (MODY) or other forms of diabetes. SUR, sulfonylurea receptor; ATP, adenosine triphosphate; ADP, adenosine diphosphate, cAMP, cyclic adenosine monophosphate. *(Adapted from WL Lowe, in JL Jameson (ed): Principles of Molecular Medicine. Totowa, NJ, Humana, 1998.)*

ACTION

Once insulin is secreted into the portal venous system, ~50% is degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS) (Fig. 338-5). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the phosphatidylinositol-3′-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

Glucose homeostasis reflects a balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (e.g., glucagon) result in integrated control of glucose supply and utilization (Chap. 339; see Fig. 339-1). In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis and reduce glucose uptake in insulin-sensitive tissues (skeletal muscle and fat),

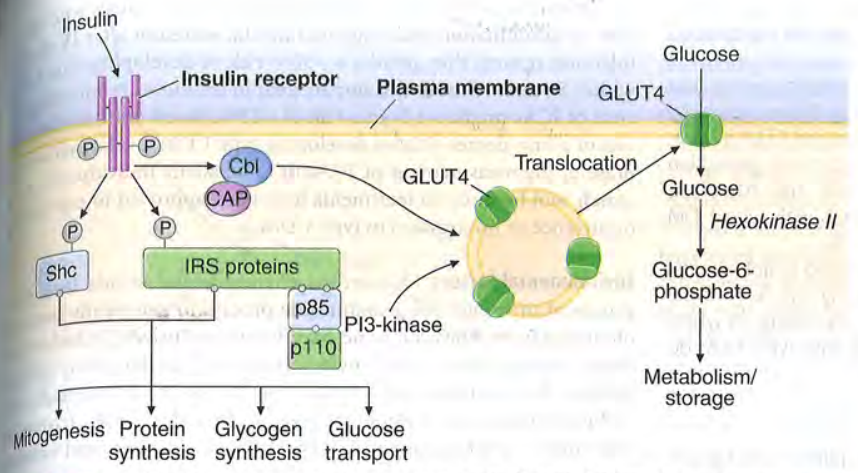


FIGURE 338-5 Insulin signal transduction pathway in skeletal muscle. The insulin receptor has intrinsic tyrosine kinase activity and interacts with insulin receptor substrates (IRS and Shc) proteins. A number of "docking" proteins bind to these cellular proteins and initiate the metabolic actions of insulin [GrB-2, SOS, SHP-2, p65, p110, and phosphatidylinositol-3′-kinase (PI-3-kinase)]. Insulin increases glucose transport through PI-3-kinase and the Cbl pathway, which promotes the translocation of intracellular vesicles containing GLUT4 glucose transporter to the plasma membrane. *(Adapted from WL Lowe, in Principles of Molecular Medicine, JL Jameson (ed). Totowa, NJ, Humana, 1998; A Virkamaki et al: J Clin Invest 103:931, 1999. For additional details see AR Saltiel, CR Kahn: Nature 414:799, 2001.)*

thereby promoting mobilization of stored precursors such as amino acids and free fatty acids (lipolysis). Glucagon, secreted by pancreatic alpha cells when blood glucose or insulin levels are low, stimulates glycogenolysis and gluconeogenesis by the liver and renal medulla. Postprandially, the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes. Insulin, an anabolic hormone, promotes the storage of carbohydrate and fat and protein synthesis. The major portion of postprandial glucose is utilized by skeletal muscle, an effect of insulin-stimulated glucose uptake. Other tissues, most notably the brain, utilize glucose in an insulin-independent fashion.

PATHOGENESIS

TYPE 1 DM

Type 1 DM is the result of interactions of genetic, environmental, and immunologic factors that ultimately lead to the destruction of the pancreatic beta cells and insulin deficiency. Type 1 DM results from autoimmune beta cell destruction and most, but not all, individuals have evidence of islet-directed autoimmunity. Some individuals who have the clinical phenotype of type 1 DM lack immunologic markers indicative of an autoimmune process involving the beta cells. These individuals are thought to develop insulin deficiency by unknown, nonimmune mechanisms and are ketosis prone; many are African American or Asian in heritage. The temporal development of type 1 DM is shown schematically as a function of beta cell mass in Fig. 338-6. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. This autoimmune process is thought to be triggered by an infectious or environmental stimulus and to be sustained by a beta cell–specific molecule. In the majority, immunologic markers appear after the triggering event but before diabetes becomes clinically overt. Beta cell mass then begins to decline, and insulin secretion becomes progressively impaired, although normal glucose tolerance is maintained. The rate of decline in beta cell mass varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until a majority of beta cells are destroyed (~80%). At this point, residual functional beta cells still exist but are insufficient in number to maintain glucose tolerance. The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements, as might occur during infections or puberty. After the initial clinical presentation of type 1 DM, a "honeymoon" phase may ensue during which time glycemic control is achieved with modest doses of insulin or, rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys the remaining beta cells, and the individual becomes completely insulin deficient.

GENETIC CONSIDERATIONS Susceptibility to type 1 DM involves multiple genes. The concordance of type 1 DM in identical twins ranges between 30 and 70%, indicating that additional modifying factors are likely involved in determining whether diabetes develops. The major susceptibility gene for type 1 DM is located in the HLA region on chromosome 6. Polymorphisms in the HLA complex account for 40–50% of the genetic risk of developing type 1 DM. This region contains genes that encode the class II MHC molecules, which present antigen to helper T cells and thus are involved in initiating the immune response (Chap. 309). The ability of class II MHC molecules to present antigen is dependent on the amino acid composition of their antigen-binding sites. Amino acid substitutions may influence the specificity of the immune response by altering the binding affinity of different antigens for class II molecules.

Most individuals with type 1 DM have the HLA DR3 and/or DR4 haplotype. Refinements in genotyping of HLA loci have shown that the haplotypes DQA1*0301, DQB1*0302, and DQB1*0201 are most strongly associated with type 1 DM. These haplotypes are present in 40% of chil-

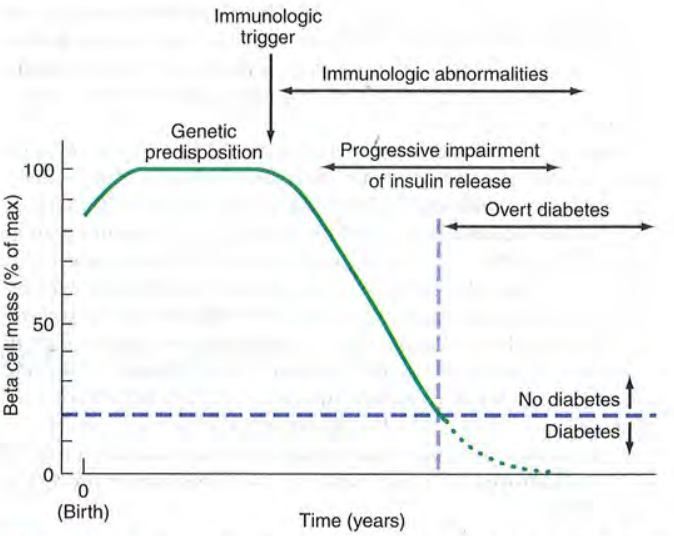


FIGURE 338-6 Temporal model for development of type 1 diabetes. Individuals with a genetic predisposition are exposed to an immunologic trigger that initiates an autoimmune process, resulting in a gradual decline in beta cell mass. The downward slope of the beta cell mass varies among individuals and may not be continuous. This progressive impairment in insulin release results in diabetes when ~80% of the beta cell mass is destroyed. A "honeymoon" phase may be seen in the first 1 or 2 years after the onset of diabetes and is associated with reduced insulin requirements. *[Adapted from Medical Management of Type 1 Diabetes, 3d ed, JS Skyler (ed). American Diabetes Association, Alexandria, VA, 1998.]*

dren with type 1 DM as compared to 2% of the normal U.S. population. However, most individuals with predisposing haplotypes do not develop diabetes.

In addition to MHC class II associations, at least 10 different genetic loci contribute susceptibility to type 1 DM (loci recently identified include polymorphisms in the promoter region of the insulin gene, the CTLA-4 gene, interleukin-2 receptor, *IFIH1*, and PTPN22). Genes that confer protection against the development of the disease also exist. The haplotype DQA1*0102, DQB1*0602 is extremely rare in individuals with type 1 DM (<1%) and appears to provide protection from type 1 DM.

Although the risk of developing type 1 DM is increased tenfold in relatives of individuals with the disease, the risk is relatively low: 3–4% if the parent has type 1 diabetes and 5–15% in a sibling (depending on which HLA haplotypes are shared). Hence, most individuals with type 1 DM do not have a first-degree relative with this disorder.

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

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

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

Environmental Factors Numerous environmental events have been proposed to trigger the autoimmune process in genetically susceptible individuals; however, none have been conclusively linked to diabetes. Identification of an environmental trigger has been difficult because the event may precede the onset of DM by several years (Fig. 338-6). Putative environmental triggers include viruses (coxsackie and rubella most prominently), bovine milk proteins, and nitrosourea compounds.

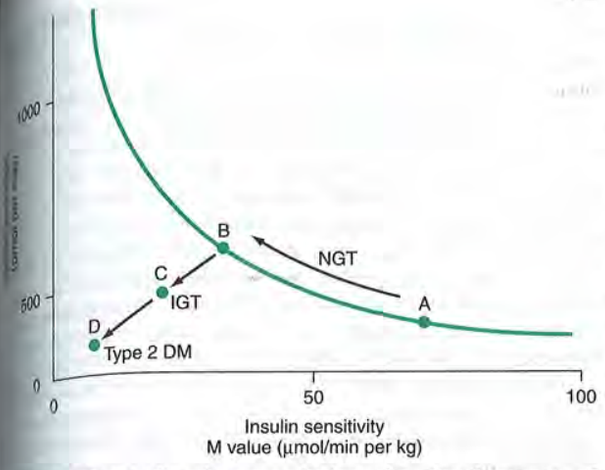
Prevention of Type 1 DM A number of interventions have successfully delayed or prevented diabetes in animal models. Some interventions have targeted the immune system directly (immunosuppression, selective T cell subset deletion, induction of immunologic tolerance to islet proteins), whereas others have prevented islet cell death by blocking cytotoxic cytokines or increasing islet resistance to the destructive process. Though results in animal models are promising, these interventions have not been successful in preventing type 1 DM in humans. The Diabetes Prevention Trial—type 1 concluded that administering insulin (IV or PO) to individuals at high risk for developing type 1 DM did not prevent type 1 DM. In patients with new-onset type 1 diabetes, treatment with anti-CD3 monoclonal antibodies has recently been shown to slow the decline in C-peptide levels.

TYPE 2 DM

Insulin resistance and abnormal insulin secretion are central to the development of type 2 DM. Although the primary defect is controversial, most studies support the view that insulin resistance precedes an insulin secretory defect but that diabetes develops only when insulin secretion becomes inadequate.

GENETIC CONSIDERATIONS Type 2 DM has a strong genetic component. The concordance of type 2 DM in identical twins is between 70 and 90%. Individuals with a parent with type 2 DM have an increased risk of diabetes; if both parents have type 2 DM, the risk approaches 40%. Insulin resistance, as demonstrated by reduced glucose utilization in skeletal muscle, is present in many nondiabetic, first-degree relatives of individuals with type 2 DM. The disease is polygenic and multifactorial since in addition to genetic susceptibility, environmental factors (such as obesity, nutrition, and physical activity) modulate the phenotype. The genes that predispose to type 2 DM are incompletely identified, but recent genome-wide association studies have identified several genes that convey a relatively small risk for type 2 DM (relative risk of 1.1-1.5). Most prominent is a variant of the transcription factor 7-like 2 gene that has been associated with type 2 diabetes in several populations and with impaired glucose tolerance in one population at high risk for diabetes. Genetic polymorphisms associated with type 2 diabetes have also been found in the genes encoding the peroxisome proliferators-activated receptor-γ, inward rectifying potassium channel expressed in beta cells, zinc transporter expressed in beta cells, IRS, and calpain 10. The mechanisms by which these genetic alterations increase the susceptibility to type 2 diabetes are not clear, but several are predicted to alter insulin secretion. Investigation using genome-wide scanning for polymorphisms associated with type 2 DM is ongoing.

Pathophysiology Type 2 DM is characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production, and abnormal fat metabolism. Obesity, particularly visceral or central (as



URE 338-7 Metabolic changes during the development of ype 2 diabetes mellitus (DM). Insulin secretion and insulin sensitiv- e related, and as an individual becomes more insulin resistant (by ng from point A to point B), insulin secretion increases. A failure ompensate by increasing the insulin secretion results initially in aired glucose tolerance (IGT; point C) and ultimately in type 2 DM nt D). *(Adapted from SE Kahn: J Clin Endocrinol Metab 86:4047, 2001; Bergman, M Ader: Trends Endocrinol Metab 11:351, 2000.)*

denced by the hip-waist ratio), is very common in type 2 DM. In early stages of the disorder, glucose tolerance remains near-nor- l, despite insulin resistance, because the pancreatic beta cells com- nsate by increasing insulin output (Fig. 338-7). As insulin resistance d compensatory hyperinsulinemia progress, the pancreatic islets in rtain individuals are unable to sustain the hyperinsulinemic state. GT, characterized by elevations in postprandial glucose, then devel- s. A further decline in insulin secretion and an increase in hepatic cose production lead to overt diabetes with fasting hyperglycemia. timately, beta cell failure may ensue.

etabolic Abnormalities • ***ABNORMAL MUSCLE AND FAT METABO-SM*** Insulin resistance, the decreased ability of insulin to act effec- ely on target tissues (especially muscle, liver, and fat), is a prominent ature of type 2 DM and results from a combination of genetic sus- ptibility and obesity. Insulin resistance is relative, however, since su- rnormal levels of circulating insulin will normalize the plasma cose. Insulin dose-response curves exhibit a rightward shift, indi- ting reduced sensitivity, and a reduced maximal response, indicating overall decrease in maximum glucose utilization (30–60% lower en in normal individuals). Insulin resistance impairs glucose utiliza- on by insulin-sensitive tissues and increases hepatic glucose output; oth effects contribute to the hyperglycemia. Increased hepatic glu- se output predominantly accounts for increased FPG levels, whereas creased peripheral glucose usage results in postprandial hyperglyce- ia. In skeletal muscle, there is a greater impairment in nonoxidative cose usage (glycogen formation) than in oxidative glucose metabo- m through glycolysis. Glucose metabolism in insulin-independent sues is not altered in type 2 DM.

The precise molecular mechanism leading to insulin resistance in pe 2 DM has not been elucidated. Insulin receptor levels and tyrosine nase activity in skeletal muscle are reduced, but these alterations are st likely secondary to hyperinsulinemia and are not a primary defect. herefore, "postreceptor" defects in insulin-regulated phosphorylation/ phosphorylation may play the predominant role in insulin resistance g. 338-5). For example, a PI-3-kinase signaling defect may reduce nslocation of GLUT4 to the plasma membrane. Other abnormalities lude the accumulation of lipid within skeletal myocytes, which may pair mitochondrial oxidative phosphorylation and reduce insulin- mulated mitochondrial ATP production. Impaired fatty acid oxidation d lipid accumulation within skeletal myocytes may generate reactive oxygen species such as lipid peroxides. Of note, not all insulin signal transduction pathways are resistant to the effects of insulin (e.g., those controlling cell growth and differentiation using the mitogenic-activated protein kinase pathway). Consequently, hyperinsulinemia may increase the insulin action through these pathways, potentially accelerating diabetes-related conditions such as atherosclerosis.

The obesity accompanying type 2 DM, particularly in a central or visceral location, is thought to be part of the pathogenic process. The increased adipocyte mass leads to increased levels of circulating free fatty acids and other fat cell products (Chap. 74). For example, adipocytes secrete a number of biologic products (nonesterified free fatty acids, retinol-binding protein 4, leptin, TNF-α, resistin, and adiponectin). In addition to regulating body weight, appetite, and energy expenditure, adipokines also modulate insulin sensitivity. The increased production of free fatty acids and some adipokines may cause insulin resistance in skeletal muscle and liver. For example, free fatty acids impair glucose utilization in skeletal muscle, promote glucose production by the liver, and impair beta cell function. In contrast, the production by adipocytes of adiponectin, an insulin-sensitizing peptide, is reduced in obesity and this may contribute to hepatic insulin resistance. Adipocyte products and adipokines also produce an inflammatory state and may explain why markers of inflammation such as IL-6 and C-reactive protein are often elevated in type 2 DM. Inhibition of inflammatory signaling pathways such as the nuclear factor κB (NFκB) pathway appears to reduce insulin resistance and improve hyperglycemia in animal models.

IMPAIRED INSULIN SECRETION Insulin secretion and sensitivity are interrelated (Fig. 338-7). In type 2 DM, insulin secretion initially increases in response to insulin resistance to maintain normal glucose tolerance. Initially, the insulin secretory defect is mild and selectively involves glucose-stimulated insulin secretion. The response to other nonglucose secretagogues, such as arginine, is preserved. Eventually, the insulin secretory defect progresses to a state of grossly inadequate insulin secretion.

The reason(s) for the decline in insulin secretory capacity in type 2 DM is unclear. The assumption is that a second genetic defect—superimposed upon insulin resistance—leads to beta cell failure. Islet amyloid polypeptide or amylin is cosecreted by the beta cell and forms the amyloid fibrillar deposit found in the islets of individuals with long-standing type 2 DM. Whether such islet amyloid deposits are a primary or secondary event is not known. The metabolic environment of diabetes may also negatively impact islet function. For example, chronic hyperglycemia paradoxically impairs islet function ("glucose toxicity") and leads to a worsening of hyperglycemia. Improvement in glycemic control is often associated with improved islet function. In addition, elevation of free fatty acid levels ("lipotoxicity") and dietary fat may also worsen islet function. Beta cell mass is decreased in individuals with long-standing type 2 diabetes.

INCREASED HEPATIC GLUCOSE AND LIPID PRODUCTION In type 2 DM, insulin resistance in the liver reflects the failure of hyperinsulinemia to suppress gluconeogenesis, which results in fasting hyperglycemia and decreased glycogen storage by the liver in the postprandial state. Increased hepatic glucose production occurs early in the course of diabetes, though likely after the onset of insulin secretory abnormalities and insulin resistance in skeletal muscle. As a result of insulin resistance in adipose tissue and obesity, free fatty acid (FFA) flux from adipocytes is increased, leading to increased lipid [very low density lipoprotein (VLDL) and triglyceride] synthesis in hepatocytes. This lipid storage or steatosis in the liver may lead to nonalcoholic fatty liver disease (Chap. 303) and abnormal liver function tests. This is also responsible for the dyslipidemia found in type 2 DM [elevated triglycerides, reduced high-density lipoprotein (HDL), and increased small dense low-density lipoprotein (LDL) particles].

Insulin Resistance Syndromes The insulin resistance condition comprises a spectrum of disorders, with hyperglycemia representing one of

the most readily diagnosed features. The *metabolic syndrome*, the *insulin resistance syndrome*, or *syndrome X* are terms used to describe a constellation of metabolic derangements that includes insulin resistance, hypertension, dyslipidemia (low HDL and elevated triglycerides), central or visceral obesity, type 2 diabetes or IGT/IFG, and accelerated cardiovascular disease. This syndrome is discussed in Chap. 236.

A number of relatively rare forms of severe insulin resistance include features of type 2 DM or IGT (Table 338-1). Acanthosis nigricans and signs of hyperandrogenism (hirsutism, acne, and oligomenorrhea in women) are also common physical features. Two distinct syndromes of severe insulin resistance have been described in adults: (1) type A, which affects young women and is characterized by severe hyperinsulinemia, obesity, and features of hyperandrogenism; and (2) type B, which affects middle-aged women and is characterized by severe hyperinsulinemia, features of hyperandrogenism, and autoimmune disorders. Individuals with the type A insulin resistance syndrome have an undefined defect in the insulin-signaling pathway; individuals with the type B insulin resistance syndrome have autoantibodies directed at the insulin receptor. These receptor autoantibodies may block insulin binding or may stimulate the insulin receptor, leading to intermittent hypoglycemia.

Polycystic ovary syndrome (PCOS) is a common disorder that affects premenopausal women and is characterized by chronic anovulation and hyperandrogenism (Chap. 341). Insulin resistance is seen in a significant subset of women with PCOS, and the disorder substantially increases the risk for type 2 DM, independent of the effects of obesity.

Prevention Type 2 DM is preceded by a period of IGT, and a number of lifestyle modifications and pharmacologic agents prevent or delay the onset of DM. The Diabetes Prevention Program (DPP) demonstrated that intensive changes in lifestyle (diet and exercise for 30 min/day five times/week) in individuals with IGT prevented or delayed the development of type 2 DM by 58% compared to placebo. This effect was seen in individuals regardless of age, sex, or ethnic group. In the same study, metformin prevented or delayed diabetes by 31% compared to placebo. The lifestyle intervention group lost 5–7% of their body weight during the 3 years of the study. Studies in Finnish and Chinese populations noted similar efficacy of diet and exercise in preventing or delaying type 2 DM; acarbose, metformin, thiazolidinediones, and orlistat prevent or delay type 2 DM but are not approved for this purpose. When administered to nondiabetic individuals for other reasons (cardiac, cholesterol lowering, etc.), pravastatin reduced the number of new cases of diabetes. Individuals with a strong family history of type 2 DM and individuals with IFG or IGT should be strongly encouraged to maintain a normal BMI and engage in regular physical activity. Pharmacologic therapy for individuals with prediabetes is currently controversial because its cost-effectiveness and safety profile are not known. A recent ADA Consensus panel concluded that metformin, but not other medications, could be considered in individuals with both IFG and IGT who are at very high risk for progression to diabetes (age < 60 years, BMI ≥ 35 kg/m^2, family history of diabetes in first-degree relative, elevated triglycerides, reduced HDL, hypertension, or A1C > 6.0%).

GENETICALLY DEFINED, MONOGENIC FORMS OF DIABETES MELLITUS

Several monogenic forms of DM have been identified. Six different variants of MODY, caused by mutations in genes encoding islet-enriched transcription factors or glucokinase (Fig. 338-4), are transmitted as autosomal dominant disorders. MODY 1, MODY 3, and MODY 5 are caused by mutations in the hepatocyte nuclear transcription factor (HNF) 4α, HNF-1α, and HNF-1β, respectively. As their names imply, these transcription factors are expressed in the liver but also in other tissues, including the pancreatic islets and kidney. These factors most likely affect islet development or the expression of genes important in glucose-stimulated insulin secretion or the maintenance of beta cell mass. For example, individuals with an HNF-1α mutation have a progressive decline in glycemic control but respond to sulfonylureas. In fact, some of these patients were initially thought to have type 1 DM but were later shown to respond to a sulfonylurea when insulin was discontinued. Individuals with a HNF-1β mutation have progressive impairment of insulin secretion, hepatic insulin resistance, and require insulin treatment (minimal response to sulfonylureas). These individual often have other abnormalities such as renal cysts, mild pancreatic exocrine insufficiency, and abnormal liver function tests. Individuals with MODY 2, the result of mutations in the glucokinase gene, have mild-to-moderate, stable hyperglycemia that does not respond to oral hypoglycemic agents. Glucokinase catalyzes the formation of glucose-6-phosphate from glucose, a reaction that is important for glucose sensing by the beta cells and for glucose utilization by the liver. As a result of glucokinase mutations, higher glucose levels are required to elicit insulin secretory responses, thus altering the set point for insulin secretion. MODY 4 is a rare variant caused by mutations in the insulin promoter factor (IPF) 1, which is a transcription factor that regulates pancreatic development and insulin gene transcription. Homozygous inactivating mutations cause pancreatic agenesis, whereas heterozygous mutations result in DM. Studies of populations with type 2 DM suggest that mutations in MODY-associated genes are rare (<5%) causes of type 2 DM.

Transient or permanent neonatal diabetes (onset < 6 months of age) may be caused by several genetic mutations and requires treatment with insulin. Mutations in subunits of the ATP-sensitive potassium channel subunits (Kir6.2 and ABCC8) (Fig. 338-4) are the major causes of permanent neonatal diabetes. Although these activating mutations impair glucose-stimulated insulin secretion, these individuals may respond to sulfonylureas and improve their glycemic control and can be treated with these agents. Homozygous glucokinase mutations cause a severe form of neonatal diabetes.

ACUTE COMPLICATIONS OF DM

Diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) are acute complications of diabetes. DKA was formerly considered a hallmark of type 1 DM, but it also occurs in individuals who lack immunologic features of type 1 DM and who can subsequently be treated with oral glucose-lowering agents (these obese individuals with type 2 DM are often of Hispanic or African-American descent). HHS is primarily seen in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and acid-base abnormalities. DKA and HHS exist along a continuum of hyperglycemia, with or without ketosis. The metabolic similarities and differences in DKA and HHS are highlighted in Table 338-4. Both disor-

TABLE 338-4 LABORATORY VALUES IN DIABETIC KETOACIDOSIS (DKA) AND HYPERGLYCEMIC HYPEROSMOLAR STATE (HHS) (REPRESENTATIVE RANGES AT PRESENTATION)

	DKA	HHS
Glucose,[a] mmol/L (mg/dL)	13.9–33.3 (250–600)	33.3–66.6 (600–1200)
Sodium, meq/L	125–135	135–145
Potassium[a]	Normal to ↑	Normal
Magnesium[a]	Normal[b]	Normal
Chloride[a]	Normal	Normal
Phosphate[a]	↓	Normal
Creatinine	Slightly ↑	Moderately ↑
Osmolality (mOsm/mL)	300–320	330–380
Plasma ketones[a]	++++	+/−
Serum bicarbonate,[a] meq/L	<15 meq/L	Normal to slightly ↓
Arterial pH	6.8–7.3	>7.3
Arterial P_{CO_2},[a] mmHg	20–30	Normal
Anion gap[a] [Na − (Cl + HCO_3)]	↑	Normal to slightly ↑

[a]Large changes occur during treatment of DKA.
[b]Although plasma levels may be normal or high at presentation, total-body stores are usually depleted.

PART 15 Endocrinology and Metabolism

TABLE 338-5 MANIFESTATIONS OF DIABETIC KETOACIDOSIS

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

Note: UTI, urinary tract infection.

ders are associated with potentially serious complications if not promptly diagnosed and treated.

DIABETIC KETOACIDOSIS

Clinical Features The symptoms and physical signs of DKA are listed in Table 338-5 and usually develop over 24 h. DKA may be the initial symptom complex that leads to a diagnosis of type 1 DM, but more frequently it occurs in individuals with established diabetes. Nausea and vomiting are often prominent, and their presence in an individual with diabetes warrants laboratory evaluation for DKA. Abdominal pain may be severe and can resemble acute pancreatitis or ruptured viscus. Hyperglycemia leads to glucosuria, volume depletion, and tachycardia. Hypotension can occur because of volume depletion in combination with peripheral vasodilatation. Kussmaul respirations and a fruity odor on the patient's breath (secondary to metabolic acidosis and increased acetone) are classic signs of the disorder. Lethargy and central nervous system depression may evolve into coma with severe DKA but should also prompt evaluation for other reasons for altered mental status (infection, hypoxia, etc.). Cerebral edema, an extremely serious complication of DKA, is seen most frequently in children. Signs of infection, which may precipitate DKA, should be sought on physical examination, even in the absence of fever. Tissue ischemia (heart, brain) can also be a precipitating factor.

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

The combination of insulin deficiency and hyperglycemia reduces the hepatic level of fructose-2,6-phosphate, which alters the activity of phosphofructokinase and fructose-1,6-bisphosphatase. Glucagon excess decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase. These changes shift the handling of pyruvate toward glucose synthesis and away from glycolysis. The increased levels of glucagon and catecholamines in the face of low insulin levels promote glycogenolysis. Insulin deficiency also reduces levels of the GLUT4 glucose transporter, which impairs glucose uptake into skeletal muscle and fat and reduces intracellular glucose metabolism (Fig. 338-5).

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

DKA is initiated by inadequate levels of plasma insulin (Table 338-5). Most commonly, DKA is precipitated by increased insulin requirements, as might occur during a concurrent illness. Failure to augment insulin therapy often compounds the problem. Occasionally, complete omission of insulin by the patient or health care team (in a hospitalized patient with type 1 DM) precipitates DKA. Patients using insulin infusion devices with short-acting insulin are at increased risk of DKA, since even a brief interruption in insulin delivery (e.g., mechanical malfunction) quickly leads to insulin deficiency.

Laboratory Abnormalities and Diagnosis The timely diagnosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia, ketosis, and metabolic acidosis (increased anion gap) along with a number of secondary metabolic derangements (Table 338-4). Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently <10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total-body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis. Total-body stores of sodium, chloride, phosphorous, and magnesium are also reduced in DKA but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.

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

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

The metabolic derangements of DKA exist along a spectrum, beginning with mild acidosis with moderate hyperglycemia evolving into more severe findings. The degree of acidosis and hyperglycemia do not necessarily correlate closely since a variety of factors determine the level of hyperglycemia (oral intake, urinary glucose loss). Ketonemia is a consistent finding in DKA and distinguishes it from simple hyperglycemia. The differential diagnosis of DKA includes starvation ketosis, alcoholic ketoacidosis (bicarbonate usually > 15 meq/L) and other increased anion gap acidosis (Chap. 48).

℞ DIABETIC KETOACIDOSIS

The management of DKA is outlined in **Table 338-6**. After initiating IV fluid replacement and insulin therapy, the agent or event that precipitated the

TABLE 338-6 MANAGEMENT OF DIABETIC KETOACIDOSIS

1. Confirm diagnosis (↑ plasma glucose, positive serum ketones, metabolic acidosis).
2. Admit to hospital; intensive-care setting may be necessary for frequent monitoring or if pH < 7.00 or unconscious.
3. Assess:
   Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, bicarbonate, phosphate)
   Acid-base status—pH, HCO_3^-, P_{CO_2}, β-hydroxybutyrate
   Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline over first 1–3 h (10–15 mL/kg per hour); subsequently, 0.45% saline at 150–300 mL/h; change to 5% glucose and 0.45% saline at 100–200 mL/h when plasma glucose reaches 250 mg/dL (14 mmol/L).
5. Administer short-acting insulin: IV (0.1 units/kg) or IM (0.3 units/kg), then 0.1 units/kg per hour by continuous IV infusion; increase 2- to 3-fold if no response by 2–4 h. If initial serum potassium is < 3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected to > 3.3 mmol/L (3.3.meq/L).
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG).
7. Measure capillary glucose every 1–2 h; measure electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every 4 h for first 24 h.
8. Monitor blood pressure, pulse, respirations, mental status, fluid intake and output every 1–4 h.
9. Replace K^+: 10 meq/h when plasma K^+ < 5.5 meq/L, ECG normal, urine flow and normal creatinine documented; administer 40–80 meq/h when plasma K^+ < 3.5 meq/L or if bicarbonate is given.
10. Continue above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved. Insulin infusion may be decreased to 0.05–0.1 units/kg per hour.
11. Administer intermediate or long-acting insulin as soon as patient is eating. Allow for overlap in insulin infusion and subcutaneous insulin injection.

Note: CXR, chest x-ray; ECG, electrocardiogram.
Source: Adapted from M Sperling, in *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 1998; and AE Kitabchi et al: Diabetes Care 29:2739, 2006.

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

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

A bolus of IV (0.1 units/kg) or IM (0.3 units/kg) short-acting insulin should be administered immediately (Table 338-6), and subsequent treatment should provide continuous and adequate levels of circulating insulin. Intravenous administration is preferred (0.1 units/kg per hour), because it assures rapid distribution and allows adjustment of the infusion rate as the patient responds to therapy. In mild episodes of DKA, short-acting insulin analogues can be used subcutaneously. Intravenous regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.05–0.1 units/kg per hour). Intermediate or long-acting insulin, in combination with SC short-acting insulin, should be administered as soon as the patient resumes eating, as this facilitates transition to an outpatient insulin regimen and reduces length of hospital stay. It is crucial to continue the insulin infusion until adequate insulin levels are achieved by the SC route. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse.

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

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

Despite a bicarbonate deficit, bicarbonate replacement is not usually necessary. In fact, theoretical arguments suggest that bicarbonate administration and rapid reversal of acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia. The results of most clinical trials do not support the routine use of bicarbonate replacement, and one study in children found that bicarbonate use was associated with an increased risk of cerebral edema. However, in the presence of severe acidosis (arterial pH < 7.0 after initial hydration), the ADA advises bicarbonate [50 mmol/L (meq/L) of sodium bicarbonate in 200 mL of sterile water with 10 meq/L KCl over 1 h if pH = 6.9–7.0; or 100 mmol/L (meq/L) of sodium bicarbonate in 400 mL of sterile water with 20 meq/L KCl over 2 h if pH < 6.9]. Repeat the dose of bicarbonate every 2 h until the arterial pH is >7.0. Hypophosphatemia may result from increased glucose usage, but randomized clinical trials have not demonstrated that phosphate replacement is beneficial in DKA. If the serum phosphate < 0.32 mmol/L (1.0 mg/dL), then phosphate supplement should be considered and the serum calcium monitored. Hypomagnesemia may develop during DKA therapy and may also require supplementation.

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

Following treatment, the physician and patient should review the sequence of events that led to DKA to prevent future recurrences. Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness. During illness or when oral intake is compromised, patients should: (1) frequently measure the capillary blood glucose; (2) measure urinary ketones when the serum glucose > 16.5 mmol/L (300 mg/dL); (3) drink fluids to maintain hydration; (4) continue or increase insulin; and (5) seek medical attention if

dehydration, persistent vomiting, or uncontrolled hyperglycemia develop. Using these strategies, early DKA can be prevented or detected and treated appropriately on an outpatient basis.

HYPERGLYCEMIC HYPEROSMOLAR STATE

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

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

Laboratory Abnormalities and Diagnosis The laboratory features in HHS are summarized in Table 338-4. Most notable are the marked hyperglycemia [plasma glucose may be >55.5 mmol/L (1000 mg/dL)], hyperosmolality (>350 mosmol/L), and prerenal azotemia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased [add 1.6 meq to measured sodium for each 5.6-mmol/L (100 mg/dL) rise in the serum glucose]. In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation.

Rx HYPERGLYCEMIC HYPEROSMOLAR STATE

Volume depletion and hyperglycemia are prominent features of both HHS and DKA. Consequently, therapy of these disorders shares several elements (Table 338-6). In both disorders, careful monitoring of the patient's fluid status, laboratory values, and insulin infusion rate is crucial. Underlying or precipitating problems should be aggressively sought and treated. In HHS, fluid losses and dehydration are usually more pronounced than in DKA due to the longer duration of the illness. The patient with HHS is usually older, more likely to have mental status changes, and more likely to have a life-threatening precipitating event with accompanying comorbidities. Even with proper treatment, HHS has a substantially higher mortality than DKA (up to 15% in some clinical series).

Fluid replacement should initially stabilize the hemodynamic status of the patient (1–3 L of 0.9% normal saline over the first 2–3 h). Because the fluid deficit in HHS is accumulated over a period of days to weeks, the rapidity of reversal of the hyperosmolar state must balance the need for free water repletion with the risk that too rapid a reversal may worsen neurologic function. If the serum sodium > 150 mmol/L (150 meq/L), 0.45% saline should be used. After hemodynamic stability is achieved, the IV fluid administration is directed at reversing the free water deficit using hypotonic fluids (0.45% saline initially then 5% dextrose in water, D_5W). The calculated free water deficit (which averages 9–10 L) should be reversed over the next 1–2 days (infusion rates of 200–300 mL/h of hypotonic solution). Potassium repletion is usually necessary and should be dictated by repeated measurements of the serum potassium. In patients taking diuretics, the potassium deficit can be quite large and may be accompanied by magnesium deficiency. Hypophosphatemia may occur during therapy and can be improved by using KPO_4 and beginning nutrition.

As in DKA, rehydration and volume expansion lower the plasma glucose initially, but insulin is also required. A reasonable regimen for HHS begins with an IV insulin bolus of 0.1 units/kg followed by IV insulin at a constant infusion rate of 0.1 units/kg per hour. If the serum glucose does not fall, increase the insulin infusion rate by twofold. As in DKA, glucose should be added to IV fluid when the plasma glucose falls to 13.9 mmol/L (250 mg/dL), and the insulin infusion rate should be decreased to 0.05–0.1 units/kg per hour. The insulin infusion should be continued until the patient has resumed eating and can be transferred to a SC insulin regimen. The patient should be discharged from the hospital on insulin, though some patients can later switch to oral glucose-lowering agents.

CHRONIC COMPLICATIONS OF DM

The chronic complications of DM affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. Chronic complications can be divided into vascular and nonvascular complications (Table 338-7). The vascular complications of DM are further subdivided into microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications [coronary artery disease (CAD), peripheral arterial disease (PAD), cerebrovascular disease]. Nonvascular complications include problems such as gastroparesis, infections, and skin changes. Long-standing diabetes may be associated with hearing loss. Whether type 2 DM in elderly individuals is associated with impaired mental function is not clear.

The risk of chronic complications increases as a function of the duration of hyperglycemia; they usually become apparent in the second decade of hyperglycemia. Since type 2 DM often has a long asymptomatic period of hyperglycemia, many individuals with type 2 DM have complications at the time of diagnosis.

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

Evidence implicating a causative role for chronic hyperglycemia in the development of macrovascular complications is less conclusive.

TABLE 338-7 CHRONIC COMPLICATIONS OF DIABETES MELLITUS

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

However, coronary heart disease events and mortality are two to four times greater in patients with type 2 DM. These events correlate with fasting and postprandial plasma glucose levels as well as with the A1C. Other factors (dyslipidemia and hypertension) also play important roles in macrovascular complications.

MECHANISMS OF COMPLICATIONS

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

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

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

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

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

Growth factors appear to play an important role in DM-related complications, and their production is increased by most of these proposed pathways. Vascular endothelial growth factor A (VEGF-A) is increased locally in diabetic proliferative retinopathy and decreases after laser photocoagulation. TGF-β is increased in diabetic nephropathy and stimulates basement membrane production of collagen and fibronectin by mesangial cells. Other growth factors, such as platelet-derived growth factor, epidermal growth factor, insulin-like growth factor I, growth hormone, basic fibroblast growth factor, and even insulin, have been suggested to play a role in DM-related complications. A possible unifying mechanism is that hyperglycemia leads to increased production of reactive oxygen species or superoxide in the mitochondria; these compounds may activate all four of the pathways described above. Although hyperglycemia serves as the initial trigger for complications of diabetes, it is still unknown whether the same pathophysiologic processes are operative in all complications or whether some pathways predominate in certain organs.

GLYCEMIC CONTROL AND COMPLICATIONS

The Diabetes Control and Complications Trial (DCCT) provided definitive proof that reduction in chronic hyperglycemia can prevent many of the early complications of type 1 DM. This large multicenter clinical trial randomized over 1400 individuals with type 1 DM to either intensive or conventional diabetes management, and prospectively evaluated the development of retinopathy, nephropathy, and neuropathy. Individuals in the intensive diabetes management group received multiple administrations of insulin each day along with extensive educational, psychological, and medical support. Individuals in the conventional diabetes management group received twice-daily insulin injections and quarterly nutritional, educational, and clinical evaluation. The goal in the former group was normoglycemia; the goal in the latter group was prevention of symptoms of diabetes. Individuals in the intensive diabetes management group achieved a substantially lower hemoglobin A1C (7.3%) than individuals in the conventional diabetes management group (9.1%).

The DCCT demonstrated that improvement of glycemic control reduced nonproliferative and proliferative retinopathy (47% reduction), microalbuminuria (39% reduction), clinical nephropathy (54% reduction), and neuropathy (60% reduction). Improved glycemic control also slowed the progression of early diabetic complications. There was a nonsignificant trend in reduction of macrovascular events during the trial (most individuals were young and had a low risk of cardiovascular disease). The results of the DCCT predicted that individuals in the intensive diabetes management group would gain 7.7 additional years of vision, 5.8 additional years free from ESRD, and 5.6 years free from lower extremity amputations. If all complications of DM were combined, individuals in the intensive diabetes management group would experience 15.3 more years of life without significant microvascular or neurologic complications of DM, compared to individuals who received standard therapy. This translates into an additional 5.1 years of life expectancy for individuals in the intensive diabetes management group. The benefit of the improved glycemic control during the DCCT persisted even after the study concluded and glycemic control worsened. For example, individuals in the intensive diabetes management group for a mean of 6.5 years had a 42–57% reduction in cardiovascular events [nonfatal myocardial infarction (MI), stroke, or death from a cardiovascular event] at a mean follow-up of 17 years, even though their subsequent glycemic control was the same as those in the conventional diabetes management group.

The benefits of an improvement in glycemic control occurred over the entire range of A1C values (Fig. 338-8), suggesting that at any A1C level, an improvement in glycemic control is beneficial. The goal of therapy is to achieve an A1C level as close to normal as possible, without subjecting the patient to excessive risk of hypoglycemia.

The United Kingdom Prospective Diabetes Study (UKPDS) studied the course of >5000 individuals with type 2 DM for >10 years. This study utilized multiple treatment regimens and monitored the effect

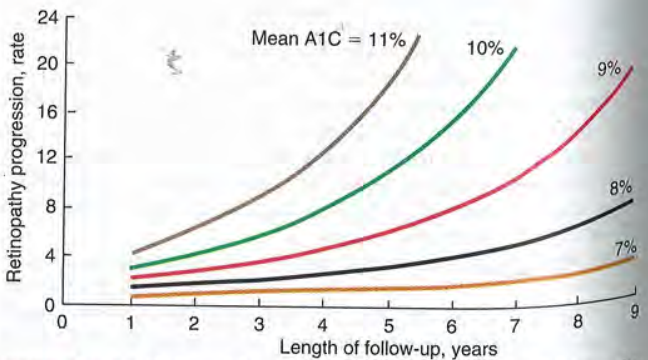


FIGURE 338-8 Relationship of glycemic control and diabetes duration to diabetic retinopathy. The progression of retinopathy in individuals in the Diabetes Control and Complications Trial is graphed as a function of the length of follow-up with different curves for different A1C values. *(Adapted from The Diabetes Control and Complications Trial Research Group: Diabetes 44:968, 1995.)*

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

One of the major findings of the UKPDS was that strict blood pressure control significantly reduced both macro- and microvascular complications. In fact, the beneficial effects of blood pressure control were greater than the beneficial effects of glycemic control. Lowering blood pressure to moderate goals (144/82 mmHg) reduced the risk of DM-related death, stroke, microvascular end points, retinopathy, and heart failure (risk reductions between 32 and 56%).

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

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

OPHTHALMOLOGIC COMPLICATIONS OF DIABETES MELLITUS

DM is the leading cause of blindness between the ages of 20 and 74 in the United States. The gravity of this problem is highlighted by the finding that individuals with DM are 25 times more likely to become legally blind than individuals without DM. Blindness is primarily the result of progressive diabetic retinopathy and clinically significant macular edema. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative. Nonproliferative diabetic retinopathy usually appears late in the first decade or early in the second decade of the disease and is marked by retinal vascular microaneurysms, blot hemorrhages, and cotton wool spots (Fig. 338-9). Mild nonproliferative retinopathy progresses to more extensive disease, characterized by changes in venous vessel caliber, intraretinal microvascular abnormalities, and more numerous microaneurysms and hemorrhages. The pathophysiologic mechanisms invoked in nonproliferative retinopathy include loss of retinal pericytes, increased retinal vascular permeability, alterations in retinal blood flow, and abnormal retinal microvasculature, all of which lead to retinal ischemia.

The appearance of neovascularization in response to retinal hypoxia is the hallmark of proliferative diabetic retinopathy (Fig. 338-9). These newly formed vessels appear near the optic nerve and/or macula and rupture easily, leading to vitreous hemorrhage, fibrosis, and ultimately retinal detachment. Not all individuals with nonproliferative retinopathy develop proliferative retinopathy, but the more severe the nonproliferative disease, the greater the chance of evolution to proliferative retinopathy within 5 years. This creates an important opportunity for early detection and treatment of diabetic retinopathy. Clinically significant macular edema can occur when only nonproliferative retinopathy is present. Fluorescein angiography is useful to detect macular edema, which is associated with a 25% chance of moderate visual loss over the next 3 years.

FIGURE 338-9 Diabetic retinopathy results in scattered hemorrhages, yellow exudates, and neovascularization. This patient has neovascular vessels proliferating from the optic disc, requiring urgent pan retinal laser photocoagulation.

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

Rx DIABETIC RETINOPATHY

The most effective therapy for diabetic retinopathy is prevention. Intensive glycemic and blood pressure control will delay the development or slow the progression of retinopathy in individuals with either type 1 or type 2 DM. Paradoxically, during the first 6–12 months of improved glycemic control, established diabetic retinopathy may transiently worsen. Fortunately, this progression is temporary, and in the long term, improved glycemic control is associated with less diabetic retinopathy. Individuals with known retinopathy are candidates for prophylactic photocoagulation when initiating intensive therapy. Once advanced retinopathy is present, improved glycemic control imparts less benefit, though adequate ophthalmologic care can prevent most blindness.

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

RENAL COMPLICATIONS OF DIABETES MELLITUS

Diabetic nephropathy is the leading cause of ESRD in the United States and a leading cause of DM-related morbidity and mortality. Both microalbuminuria and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy.

Like other microvascular complications, the pathogenesis of diabetic nephropathy is related to chronic hyperglycemia. The mechanisms by which chronic hyperglycemia leads to ESRD, though incompletely defined, involve the effects of soluble factors (growth factors, angiotensin II, endothelin, AGEs), hemodynamic alterations in the renal microcirculation (glomerular hyperfiltration or hyperper-

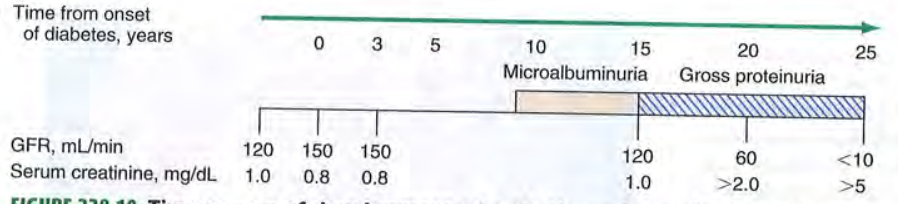


FIGURE 338-10 Time course of development of diabetic nephropathy. The relationship of time from onset of diabetes, the glomerular filtration rate (GFR), and the serum creatinine are shown. *(Adapted from RA DeFranzo, in Therapy for Diabetes Mellitus and Related Disorders, 3d ed. American Diabetes Association, Alexandria, VA, 1998.)*

fusion, increased glomerular capillary pressure), and structural changes in the glomerulus (increased extracellular matrix, basement membrane thickening, mesangial expansion, fibrosis). Some of these effects may be mediated through angiotensin II receptors. Smoking accelerates the decline in renal function. Because only 20–40% of patients with diabetes develop diabetic nephropathy, additional susceptibility factors remain unidentified. One known risk factor is a family history of diabetic nephropathy.

The natural history of diabetic nephropathy is characterized by a fairly predictable sequence of events that was initially defined for individuals with type 1 DM but appears to be similar in type 2 DM (Fig. 338-10). Glomerular hyperperfusion and renal hypertrophy occur in the first years after the onset of DM and are associated with an increase of the glomerular filtration rate (GFR). During the first 5 years of DM, thickening of the glomerular basement membrane, glomerular hypertrophy, and mesangial volume expansion occur as the GFR returns to normal. After 5–10 years of type 1 DM, ~40% of individuals begin to excrete small amounts of albumin in the urine. Microalbuminuria is defined as 30–300 mg/d in a 24-h collection or 30–300 μg/mg creatinine in a spot collection (preferred method). Although the appearance of microalbuminuria in type 1 DM is an important risk factor for progression to overt proteinuria (>300 mg/d), only ~50% of individuals progress to macroalbuminuria over the next 10 years. In some individuals with type 1 diabetes and microalbuminuria of short duration, the microalbuminuria regresses. Once macroalbuminuria is present, there is a steady decline in GFR, and ~50% of individuals reach ESRD in 7–10 years. Once macroalbuminuria develops, blood pressure rises slightly and the pathologic changes are likely irreversible. Some individuals with type 1 or type 2 DM have a decline in GFR in the absence of micro- or macroalbuminuria and this is the basis for assessing the GFR on an annual basis using serum creatinine.

The nephropathy that develops in type 2 DM differs from that of type 1 DM in the following respects: (1) microalbuminuria or macroalbuminuria may be present when type 2 DM is diagnosed, reflecting its long asymptomatic period; (2) hypertension more commonly accompanies microalbuminuria or macroalbuminuria in type 2 DM; and (3) microalbuminuria may be less predictive of diabetic nephropathy and progression to macroalbuminuria in type 2 DM. Finally, it should be noted that albuminuria in type 2 DM may be secondary to factors unrelated to DM, such as hypertension, congestive heart failure (CHF), prostate disease, or infection. Diabetic nephropathy and ESRD secondary to DM develop more commonly in African Americans, Native Americans, and Hispanic individuals than in Caucasians with type 2 DM.

Type IV renal tubular acidosis (hyporeninemic hypoaldosteronism) may occur in type 1 or 2 DM. These individuals develop a propensity to hyperkalemia, which may be exacerbated by medications [especially angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs)]. Patients with DM are predisposed to radiocontrast-induced nephrotoxicity. Risk factors for radiocontrast-induced nephrotoxicity are preexisting nephropathy and volume depletion. Individuals with DM undergoing radiographic procedures with contrast dye should be well hydrated before and after dye exposure, and the serum creatinine should be monitored for 24 h following the procedure.

℞ DIABETIC NEPHROPATHY

The optimal therapy for diabetic nephropathy is prevention by control of glycemia. As part of comprehensive diabetes care, microalbuminuria should be detected at an early stage when effective therapies can be instituted. The recommended strategy for detecting microalbuminuria is outlined in **Fig. 338-11** and includes annual measurement of the serum creatinine to estimate GFR. Interventions effective in slowing progression from microalbuminuria to macroalbuminuria include: (1) normalization of glycemia, (2) strict blood pressure control, and (3) administration of ACE inhibitors or ARBs. Dyslipidemia should also be treated.

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

Many individuals with type 1 or type 2 DM develop hypertension. Numerous studies in both type 1 and type 2 DM demonstrate the effectiveness of strict blood pressure control in reducing albumin excretion and slowing the decline in renal function. Blood pressure should be maintained at <130/80 mmHg in diabetic individuals without proteinuria. A slightly lower blood pressure (125/75) should be considered for individuals with microalbuminuria or macroalbuminuria (see "Hypertension," below).

Either ACE inhibitors or ARBs should be used to reduce the progression from microalbuminuria to macroalbuminuria and the associated decline in GFR that accompanies macroalbuminuria in individuals with type 1 or type 2 DM (see "Hypertension," below). Although direct comparisons of ACE inhibitors and ARBs are lacking, most experts believe that the two classes of drugs are equivalent in the patient with diabetes. ARBs can be used as an alternative in patients who develop ACE inhibitor–associated cough or angioedema. After 2–3 months of therapy in patients with microalbuminuria, the drug dose is increased until either the microalbuminuria disappears or the maximum dose is reached. If use of either ACE inhibitors or ARBs is not possible, then calcium channel blockers (non-dihydropyridine class), beta blockers, or diuretics should be used. However, their efficacy in slowing the fall in the GFR is not

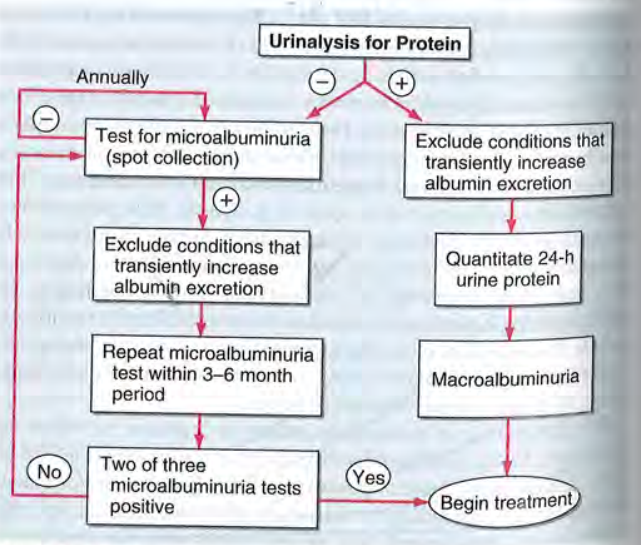


FIGURE 338-11 Screening for microalbuminuria should be performed in patients with type 1 diabetes for ≥ 5 years, in patients with type 2 diabetes, and during pregnancy. Non-diabetes-related conditions that might increase microalbuminuria are urinary tract infection, hematuria, heart failure, febrile illness, severe hyperglycemia, severe hypertension, and vigorous exercise. *(Adapted from RA DeFronzo, in Therapy for Diabetes Mellitus and Related Disorders, 3d ed. American Diabetes Association, Alexandria, VA, 1998.)*

proven. Blood pressure control with any agent is extremely important, but a drug-specific benefit in diabetic nephropathy, independent of blood pressure control, has been shown only for ACE inhibitors and ARBs in patients with DM.

The ADA suggests modest restriction of protein intake in diabetic individuals with microalbuminuria (0.8 g/kg per day) or macroalbuminuria (<0.8 g/kg per day, which is the adult Recommended Daily Allowance, or ~10% of the daily caloric intake).

Nephrology consultation should be considered when the estimated GFR < 60 mL/min per 1.743 m^2. Once macroalbuminuria ensues, the likelihood of ESRD is very high. As compared to nondiabetic individuals, hemodialysis in patients with DM is associated with more frequent complications, such as hypotension (due to autonomic neuropathy or loss of reflex tachycardia), more difficult vascular access, and accelerated progression of retinopathy. Survival after the onset of ESRD is shorter in the diabetic population compared to nondiabetics with similar clinical features. Atherosclerosis is the leading cause of death in diabetic individuals on dialysis, and hyperlipidemia should be treated aggressively. Renal transplantation from a living-related donor is the preferred therapy but requires chronic immunosuppression. Combined pancreas-kidney transplant offers the promise of normoglycemia and freedom from dialysis.

NEUROPATHY AND DIABETES MELLITUS

Diabetic neuropathy occurs in ~50% of individuals with long-standing type 1 and type 2 DM. It may manifest as polyneuropathy, mononeuropathy, and/or autonomic neuropathy. As with other complications of DM, the development of neuropathy correlates with the duration of diabetes and glycemic control. Additional risk factors are BMI (the greater the BMI, the greater the risk of neuropathy) and smoking. The presence of cardiovascular disease, elevated triglycerides, and hypertension is also associated with diabetic peripheral neuropathy. Both myelinated and unmyelinated nerve fibers are lost. Because the clinical features of diabetic neuropathy are similar to those of other neuropathies, the diagnosis of diabetic neuropathy should be made only after other possible etiologies are excluded (Chap. 379). The ADA recommends screening for distal symmetric neuropathy beginning with the initial diagnosis of diabetes and screening for autonomic neuropathy 5 years after diagnosis of type 1 DM and at the time of diagnosis of type 2 DM. All individuals with diabetes should then be screened annually for both forms of neuropathy.

Polyneuropathy/Mononeuropathy The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss, but up to 50% of patients do not have symptoms of neuropathy. Hyperesthesia, paresthesia, and dysesthesia also may occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms may include a sensation of numbness, tingling, sharpness, or burning that begins in the feet and spreads proximally. Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting <12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

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

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

Autonomic Neuropathy Individuals with long-standing type 1 or 2 DM may develop signs of autonomic dysfunction involving the cholinergic, noradrenergic, and peptidergic (peptides such as pancreatic polypeptide, substance P, etc.) systems. DM-related autonomic neuropathy can involve multiple systems, including the cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems. Autonomic neuropathies affecting the cardiovascular system cause a resting tachycardia and orthostatic hypotension. Reports of sudden death have also been attributed to autonomic neuropathy. Gastroparesis and bladder-emptying abnormalities are often caused by the autonomic neuropathy seen in DM (discussed below). Hyperhidrosis of the upper extremities and anhidrosis of the lower extremities result from sympathetic nervous system dysfunction. Anhidrosis of the feet can promote dry skin with cracking, which increases the risk of foot ulcers. Autonomic neuropathy may reduce counterregulatory hormone release, leading to an inability to sense hypoglycemia appropriately (hypoglycemia unawareness; Chap. 339), thereby subjecting the patient to the risk of severe hypoglycemia and complicating efforts to improve glycemic control.

℞ DIABETIC NEUROPATHY

Treatment of diabetic neuropathy is less than satisfactory. Improved glycemic control should be aggressively pursued and will improve nerve conduction velocity, but symptoms of diabetic neuropathy may not necessarily improve. Efforts to improve glycemic control may be confounded by autonomic neuropathy and hypoglycemia unawareness. Risk factors for neuropathy such as hypertension and hypertriglyceridemia should be treated. Avoidance of neurotoxins (alcohol) and smoking, supplementation with vitamins for possible deficiencies (B_{12}, folate; Chap. 71), and symptomatic treatment are the mainstays of therapy. Loss of sensation in the foot places the patient at risk for ulceration and its sequelae; consequently, prevention of such problems is of paramount importance. Patients with symptoms or signs of neuropathy (see "Physical Examination," below) should check their feet daily and take precautions (footwear) aimed at preventing calluses or ulcerations. If foot deformities are present, a podiatrist should be involved.

Chronic, painful diabetic neuropathy is difficult to treat but may respond to antidepressants (tricyclic antidepressants such as amitriptyline, desipramine, nortriptyline, imipramine or selective serotonin norepinephrine reuptake inhibitors such as duloxetine) or anticonvulsants (gabapentin, pregabalin, carbamazepine, lamotrigine). Two agents, duloxetine and pregabalin, have been approved by the U.S. Food and Drug Administration (FDA) for pain associated with diabetic neuropathy. However, pending further study, most recommend beginning with other agents such as a tricyclic antidepressant and switching if there is no response or if side effects develop. Aldose reductase inhibitors do not offer significant symptomatic relief. Referral to a pain management center may be necessary. Since the pain of acute diabetic neuropathy may resolve over time, medications may be discontinued as progressive neuronal damage from DM occurs.

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

GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Long-standing type 1 and 2 DM may affect the motility and function of gastrointestinal (GI) and genitourinary systems. The most prominent GI symptoms are delayed gastric emptying (gastroparesis) and altered small- and large-bowel motility (constipation or diarrhea). Gastropare-

sis may present with symptoms of anorexia, nausea, vomiting, early satiety, and abdominal bloating. Microvascular complications (retinopathy and neuropathy) are usually present. Nuclear medicine scintigraphy after ingestion of a radiolabeled meal is the best study to document delayed gastric emptying, but may not correlate well with symptoms. Noninvasive "breath tests" following ingestion of a radiolabeled meal are under development. Though parasympathetic dysfunction secondary to chronic hyperglycemia is important in the development of gastroparesis, hyperglycemia itself also impairs gastric emptying. Nocturnal diarrhea, alternating with constipation, is a feature of DM-related GI autonomic neuropathy. In type 1 DM, these symptoms should also prompt evaluation for celiac sprue because of its increased frequency. Esophageal dysfunction in long-standing DM may occur but is usually asymptomatic.

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

Erectile dysfunction and retrograde ejaculation are very common in DM and may be one of the earliest signs of diabetic neuropathy (Chap. 49). Erectile dysfunction, which increases in frequency with the age of the patient and the duration of diabetes, may occur in the absence of other signs of diabetic autonomic neuropathy.

Rx GASTROINTESTINAL/GENITOURINARY DYSFUNCTION

Current treatments for these complications of DM are inadequate. Improved glycemic control should be a primary goal, as some aspects (neuropathy, gastric function) may improve. Smaller, more frequent meals that are easier to digest (liquid) and low in fat and fiber may minimize symptoms of gastroparesis. Agents with some efficacy include dopamine agonists metoclopramide, 5–10 mg, and domperidone, 10–20 mg, before each meal. Erythromycin interacts with the motilin receptor and may promote gastric emptying. Diabetic diarrhea in the absence of bacterial overgrowth is treated symptomatically with loperamide and may respond to octreotide (50–75 μg three times daily, SC). Treatment of bacterial overgrowth with antibiotics is sometimes useful (Chap. 288).

Diabetic cystopathy should be treated with timed voiding or self-catheterization, possibly with the addition of bethanechol. Drugs that inhibit type 5 phosphodiesterase are effective for erectile dysfunction, but their efficacy in individuals with DM is slightly lower than in the nondiabetic population (Chap. 49). Sexual dysfunction in women may be improved with use of vaginal lubricants, treatment of vaginal infections, and systemic or local estrogen replacement.

CARDIOVASCULAR MORBIDITY AND MORTALITY

Cardiovascular disease is increased in individuals with type 1 or type 2 DM. The Framingham Heart Study revealed a marked increase in PAD, CHF, CAD, MI, and sudden death (risk increase from one- to fivefold) in DM. The American Heart Association has designated DM as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). Type 2 diabetes patients without a prior MI have a similar risk for coronary artery–related events as nondiabetic individuals who have had a prior MI. Because of the extremely high prevalence of underlying cardiovascular disease in individuals with diabetes (especially in type 2 DM), evidence of atherosclerotic vascular disease (e.g., cardiac stress test) should be sought in an individual with diabetes who has symptoms suggestive of cardiac ischemia, peripheral or carotid arterial disease, a resting electrocardiogram indicative of prior infarction, plans to initiate an exercise program, proteinuria, or two other cardiac risk factors (ADA recommendations). Whether and how to screen asymptomatic individuals with diabetes for CAD is controversial. The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures. The prognosis for individuals with diabetes who have CAD or MI is worse than for nondiabetics. CAD is more likely to involve multiple vessels in individuals with DM.

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

Evidence that improved glycemic control reduces cardiovascular complications in DM is inconclusive. In the DCCT, the number of cardiovascular events in patients with type 1 diabetes did not differ between the standard and intensively treated groups during the trial but were reduced at follow-up 17 years later (see above). An improvement in the lipid profile of individuals in the intensive group (lower total and LDL cholesterol, lower triglycerides) during intensive diabetes management was noted. Trials to examine whether improved glycemic control reduces cardiovascular events in type 2 diabetes are underway. Concerns about the atherogenic potential of insulin remain, since in nondiabetic individuals, higher serum insulin levels (indicative of insulin resistance) are associated with a greater risk of cardiovascular morbidity and mortality. In the UKPDS, improved glycemic control did not conclusively reduce cardiovascular mortality. Importantly, treatment with insulin and the sulfonylureas did not appear to increase the risk of cardiovascular disease in individuals with type 2 DM, refuting prior claims about the atherogenic potential of these agents.

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

Rx CARDIOVASCULAR DISEASE

In general, the treatment of coronary disease is not different in the diabetic individual (Chap. 237). Revascularization procedures for CAD, including percutaneous coronary interventions (PCI) and coronary artery bypass grafting (CABG), may be less efficacious in the diabetic individual. Initial success rates of PCI in diabetic individuals are similar to those in the nondiabetic population, but diabetic patients have higher rates of restenosis and lower long-term patency and survival rates in older studies. More recently, the use of drug-eluting stents and a GPIIb/IIIa platelet inhibitor has improved the outcomes in diabetic patients, and whether there is a difference in efficacy of PCI in diabetic individuals is not clear. Although CABG may be preferred over PCI in diabetic individuals with multivessel CAD or recent Q-wave MI, PCI is preferred in patients with single-vessel CAD or two-vessel disease (no involvement of left anterior descending).

The ADA has emphasized the importance of glycemic control and aggressive cardiovascular risk modification in all individuals with DM (see below). Past trepidation about using beta blockers in individuals who have diabetes should not prevent use of these agents since they clearly benefit diabetic patients after MI. ACE inhibitors (or ARBs) may also be particularly beneficial and should be considered in individuals with type 2 DM and other risk factors (smoking, dyslipidemia, history of cardiovascular disease, microalbuminuria). Patients with atypical chest pain or an abnormal resting EKG should be screened for CHD. Screening of asymptomatic individuals with diabetes is controversial.

antiplatelet therapy reduces cardiovascular events in individuals with who have CAD. Current recommendations by the ADA include the use aspirin for secondary prevention of coronary events. Although data monstrating efficacy in primary prevention of coronary events in DM are ing, antiplatelet therapy should be strongly considered, especially in betic individuals >30 years of age with other coronary risk factors such as hypertension, smoking, family history, or dyslipidemia. The aspirin dose 75–162 mg) is the same as that in nondiabetic individuals. Aspirin therapy does not have detrimental effects on renal function or hypertension, nor does it influence the course of diabetic retinopathy.

Cardiovascular Risk Factors • ***DYSLIPIDEMIA*** Individuals with DM may have several forms of dyslipidemia (Chap. 350). Because of the additive cardiovascular risk of hyperglycemia and hyperlipidemia, lipid abnormalities should be assessed aggressively and treated as part of comprehensive diabetes care (Fig. 338-12). The most common pattern of dyslipidemia is hypertriglyceridemia and reduced HDL cholesterol levels. DM itself does not increase levels of LDL, but the small dense LDL particles found in type 2 DM are more atherogenic because they are more easily glycated and susceptible to oxidation.

Almost all treatment studies of diabetic dyslipidemia have been performed in individuals with type 2 DM because of the greater frequency of dyslipidemia in this form of diabetes. Interventional studies have shown that the beneficial effects of LDL reduction are similar in the diabetic and nondiabetic populations. Large prospective trials of primary and secondary intervention for CHD have included some individuals with type 2 DM, and subset analyses have consistently found that reductions in LDL reduce cardiovascular events and morbidity in individuals with DM. Most clinical trials used HMG CoA reductase inhibitors, although gemfibrozil is also beneficial. No prospective studies have addressed similar questions in individuals with type 1 DM. Since the frequency of cardiovascular disease is low in children and young adults with diabetes, assessment of CV risk should be incorporated into the guidelines discussed below.

Based on the guidelines provided by the ADA and the American Heart Association, priorities in the treatment of hyperlipidemia are: (1) lower the LDL cholesterol, (2) raise the HDL cholesterol, and (3) decrease the triglycerides. A treatment strategy depends on the pattern of lipoprotein abnormalities (Fig. 338-12). Initial therapy for all forms of dyslipidemia should include dietary changes, as well as the same life-style modifications recommended in the nondiabetic population (smoking cessation, blood pressure control, weight loss, increased physical activity). The dietary recommendations for individuals with DM are similar to those advocated by the National Cholesterol Education Program (Chap. 350) and include increased monounsaturated fat and carbohydrates and reduced saturated fats and cholesterol. Though viewed as important, the response to dietary alterations is often modest (<10% reduction in the LDL). Improvement in glycemic control will lower triglycerides and have a modest beneficial effect by raising HDL. HMG CoA reductase inhibitors are the agents of choice for lowering the LDL. According to guidelines of the ADA and the American Heart Association, the target lipid values in diabetic individuals (age >40 years) without cardiovascular disease should be: LDL < 2.6 mmol/L (100 mg/dL); HDL > 1.1 mmol/L (40 mg/dL) in men and >1.38 mmol/L (50 mg/dL) in women; and triglycerides < 1.7 mmol/L (150 mg/dL). The rationale for these goals is that the risk of CHD is similar to that in patients without diabetes who have had a prior MI. In patients >40 years, the ADA recommends addition of statin, regardless of the LDL, to reduce LDL by 30–40%. If the patient is known to have cardiovascular disease, the ADA recommends an LDL goal of <1.8 mmol/L (70 mg/dL) as an "option" [in keeping with evidence that such a goal is beneficial in non-diabetic individuals with CAD (Chap. 350)]. Fibrates have some efficacy and should be considered when the HDL is low in the setting of a mild elevation of the LDL. Combination therapy with an HMG CoA reductase inhibitor and a fibrate or another lipid-lowering agent (ezetimibe, niacin) may be needed to reach LDL or HDL goals, but statin/fibrate combinations increase the possibility of side effects such as myositis. Nicotinic acid effectively raises HDL and can be used in patients with diabetes, but high doses (>2 g/d) may worsen glycemic control and increase insulin resistance. Bile acid–binding resins should not be used if hypertriglyceridemia is present. Pharmacologic therapy of dyslipidemia to achieve a LDL < 2.6 mmol/L (100 mg/dL) should be considered in diabetic individuals <40 years of age without cardiovascular disease if the individual also has other risk factors.

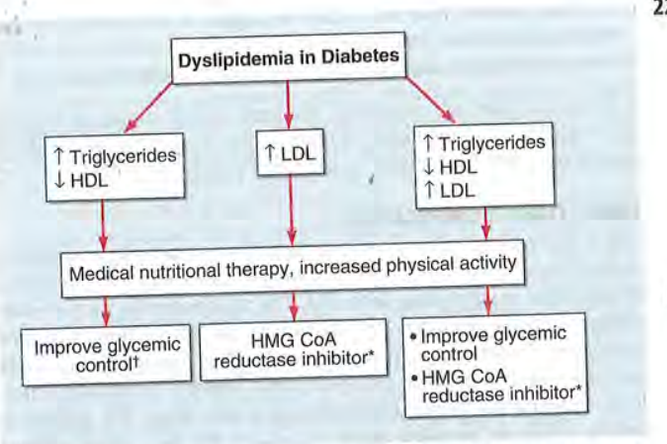


FIGURE 338-12 Dyslipidemia management in diabetes. *Second-line treatment: fibric acid derivative, ezetimibe, niacin, or bile acid–binding resin. †See text for pharmacologic treatment based on age and risk profile. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

HYPERTENSION Hypertension can accelerate other complications of DM, particularly cardiovascular disease and nephropathy. In targeting the goal of BP < 130/80, therapy should first emphasize life-style modifications such as weight loss, exercise, stress management, and sodium restriction. Realizing that more than one agent is usually required to reach a blood pressure goal, the ADA recommends that all patients with diabetes and hypertension be treated with an ACE inhibitor or an ARB. Subsequently, agents that reduce cardiovascular risk (beta blockers, thiazide diuretics, and calcium channel blockers) should be incorporated into the regimen. While ACE inhibitors and ARBs are likely equivalent in most patients with diabetes and renal disease, the ADA recommends: (1) in patients with type 1 diabetes, hypertension, and micro- or macroalbuminuria, an ACE inhibitor slowed progression of nephropathy; (2) in patients with type 2 diabetes, hypertension, and microalbuminuria, an ACE inhibitor or an ARB slowed the progression to macroalbuminuria; and (3) in patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency, an ARB slowed the decline in GFR. Additional points of emphasis include:

1. ACE inhibitors are either glucose- and lipid-neutral or glucose- and lipid-beneficial and thus positively impact the cardiovascular risk profile. Calcium channel blockers, central adrenergic antagonists, and vasodilators are lipid- and glucose-neutral.
2. Beta blockers and thiazide diuretics can increase insulin resistance and negatively impact the lipid profile; beta blockers may slightly increase the risk of developing type 2 DM. Although often questioned because of the potential masking of hypoglycemic symptoms, beta blockers are safe in most patients with diabetes and reduce cardiovascular events.
3. Sympathetic inhibitors and α-adrenergic blockers may worsen orthostatic hypotension in the diabetic individual with autonomic neuropathy.
4. Equivalent reduction in blood pressure by different classes of agents may not translate into equivalent protection from cardiovascular and renal endpoints. Thiazides, beta blockers, ACE inhibitors, and ARBs positively impact cardiovascular endpoints (MI or stroke).
5. Non-dihydropyridine calcium channel blockers (verapamil and diltiazem), rather than dihydropyridine agents (amlodipine and nifedipine), are preferred in diabetics.

6. A blood pressure goal of <125/75 is suggested for individuals with macroalbuminuria, hypertension, and diabetes.
7. Serum potassium and renal function should be monitored.

Because of the high prevalence of atherosclerotic disease in individuals with DM, the possibility of renovascular hypertension should be considered when the blood pressure is not readily controlled.

LOWER EXTREMITY COMPLICATIONS

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

Approximately 15% of individuals with DM develop a foot ulcer (great toe or MTP areas are most common), and a significant subset will ultimately undergo amputation (14–24% risk with that ulcer or subsequent ulceration). Risk factors for foot ulcers or amputation include: male sex, diabetes >10 years' duration, peripheral neuropathy, abnormal structure of foot (bony abnormalities, callus, thickened nails), peripheral arterial disease, smoking, history of previous ulcer or amputation, and poor glycemic control. Large callouses are often precursors to or overlie ulcerations.

Rx LOWER EXTREMITY COMPLICATIONS

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

Despite preventive measures, foot ulceration and infection are common and represent a serious problem. Due to the multifactorial pathogenesis of lower extremity ulcers, management of these lesions is multidisciplinary and often demands expertise in orthopedics, vascular surgery, endocrinology, podiatry, and infectious diseases. The plantar surface of the foot is the most common site of ulceration. Ulcers may be primarily neuropathic (no accompanying infection) or may have surrounding cellulitis or osteomyelitis. Cellulitis without ulceration is also frequent and should be treated with antibiotics that provide broad-spectrum coverage, including anaerobes (see below).

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

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

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

Mild or non-limb-threatening infections can be treated with oral antibiotics (cephalosporin, clindamycin, amoxicillin/clavulanate, and fluoroquinolones), surgical debridement of necrotic tissue, local wound care (avoidance of weight bearing over the ulcer), and close surveillance for progression of infection. More severe ulcers may require IV antibiotics as well as bed rest and local wound care. Urgent surgical debridement may be required. Strict control of glycemia should be a goal (see below). Intravenous antibiotics should provide broad-spectrum coverage directed toward *Staphylococcus aureus*, streptococci, gram-negative aerobes, and anaerobic bacteria. Initial antimicrobial regimens include ertapenem, piperacillin/tazobactam, cefotetan, ampicillin/sulbactam, linezolid, or the combination of clindamycin and a fluoroquinolone. Severe infections, or infections that do not improve after 48 h of antibiotic therapy, require expansion of antimicrobial therapy to treat methicillin-resistant *S. aureus* (e.g., vancomycin) and *Pseudomonas aeruginosa*. If the infection surrounding the ulcer is not improving with IV antibiotics, reassessment of antibiotic coverage and reconsideration of the need for surgical debridement or revascularization are indicated. With clinical improvement, oral antibiotics and local wound care can be continued on an outpatient basis with close follow-up.

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

INFECTIONS

Individuals with DM have a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia, as well as diminished vascularization. Hyperglycemia aids the colonization and growth of a variety of organisms (*Candida* and other fungal species). Many common infections are more frequent and severe in the diabetic population, whereas several rare infections

be seen almost exclusively in the diabetic population. Examples of this latter category include rhinocerebral mucormycosis, emphysematous infections of the gall bladder and urinary tract, and "malignant" or invasive otitis externa. Invasive otitis externa is usually secondary to *P. aeruginosa* infection in the soft tissue surrounding the external auditory canal, usually begins with pain and discharge, and may rapidly progress to osteomyelitis and meningitis. These infections should be thought, in particular, in patients presenting with HHS.

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

DERMATOLOGIC MANIFESTATIONS

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

APPROACH TO THE PATIENT: Diabetes Mellitus

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

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

In a patient with established DM, the initial assessment should also include special emphasis on prior diabetes care, including the type of therapy, prior hemoglobin A1C levels, self-monitoring blood glucose results, frequency of hypoglycemia, presence of DM-specific complications, assessment of the patient's knowledge about diabetes, exercise, and nutrition. The chronic complications may afflict several organ systems, and an individual patient may exhibit some, all, or none of the symptoms related to the complications of DM (see above). In addition, the presence of DM-related comorbidities should be sought (cardiovascular disease, hypertension, dyslipidemia).

PHYSICAL EXAMINATION In addition to a complete physical examination, special attention should be given to DM-relevant aspects such as weight or BMI, retinal examination, orthostatic blood pressure, foot examination, peripheral pulses, and insulin injection sites. Blood pressure > 130/80 mmHg is considered hypertension in individuals with diabetes. Careful examination of the lower extremities should seek evidence of peripheral neuropathy, calluses, superficial fungal infections, nail disease, ankle reflexes, and foot deformities (such as hammer or claw toes and Charcot foot) in order to identify sites of potential skin ulceration. Vibratory sensation (128-MHz tuning fork at the base of the great toe), the ability to sense touch with a monofilament (5.07, 10-g monofilament), and pinprick sensation are useful to detect moderately advanced diabetic neuropathy. Since periodontal disease is more frequent in DM, the teeth and gums should also be examined.

CLASSIFICATION OF DM IN AN INDIVIDUAL PATIENT The etiology of diabetes in an individual with new-onset disease can usually be assigned on the basis of clinical criteria. Individuals with type 1 DM tend to have the following characteristics: (1) onset of disease prior to age 30; (2) lean body habitus; (3) requirement of insulin as the initial therapy; (4) propensity to develop ketoacidosis; and (5) an increased risk of other autoimmune disorders such as autoimmune thyroid disease, adrenal insufficiency, pernicious anemia, celiac disease, and vitiligo. In contrast, individuals with type 2 DM often exhibit the following features: (1) develop diabetes after the age of 30; (2) are usually obese (80% are obese, but elderly individuals may be lean); (3) may not require insulin therapy initially; and (4) may have associated conditions such as insulin resistance, hypertension, cardiovascular disease, dyslipidemia, or PCOS. In type 2 DM, insulin resistance is often associated with abdominal obesity (as opposed to hip and thigh obesity) and hypertriglyceridemia. Although most individuals diagnosed with type 2 DM are older, the age of diagnosis is declining, and there is a marked increase among overweight children and adolescents. Some individuals with phenotypic type 2 DM present with DKA but lack autoimmune markers and may be later treated with oral glucose-lowering agents rather than insulin (have been termed *ketosis-prone type 2 DM*). On the other hand, some individuals (5–10%) with the phenotypic appearance of type 2 DM do not have absolute insulin deficiency but have autoimmune markers (ICA, GAD autoantibodies) suggestive of type 1 DM (termed *latent autoimmune diabetes of the adult*). Such individuals are more likely to be <50 years of age, have a normal BMI, and have a personal or family history of other autoimmune disease. They are much more likely to require insulin treatment within 5 years. However, it is remains dif-

ficult to categorize some patients unequivocally. Individuals who deviate from the clinical profile of type 1 and type 2 DM, or who have other associated defects such as deafness, pancreatic exocrine disease, and other endocrine disorders, should be classified accordingly (Table 338-1).

LABORATORY ASSESSMENT The laboratory assessment should first determine whether the patient meets the diagnostic criteria for DM (Table 338-2) and then assess the degree of glycemic control (A1C, discussed below). In addition to the standard laboratory evaluation, the patient should be screened for DM-associated conditions (e.g., microalbuminuria, dyslipidemia, thyroid dysfunction). Individuals at high risk for cardiovascular disease should be screened for asymptomatic CAD by appropriate cardiac stress testing, when indicated.

The classification of the type of DM may be facilitated by laboratory assessments. Serum insulin or C-peptide measurements do not always distinguish type 1 from type 2 DM, but a low C-peptide level confirms a patient's need for insulin. Many individuals with new-onset type 1 DM retain some C-peptide production. Measurement of islet cell antibodies at the time of diabetes onset may be useful if the type of DM is not clear based on the characteristics described above.

LONG-TERM TREATMENT

OVERALL PRINCIPLES

The goals of therapy for type 1 or type 2 DM are to: (1) eliminate symptoms related to hyperglycemia, (2) reduce or eliminate the long-term microvascular and macrovascular complications of DM, and (3) allow the patient to achieve as normal a lifestyle as possible. To reach these goals, the physician should identify a target level of glycemic control for each patient, provide the patient with the educational and pharmacologic resources necessary to reach this level, and monitor/treat DM-related complications. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL), and thus most DM treatment focuses on achieving the second and third goals. The treatment goals for patients with diabetes are summarized in Table 338-8.

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

TABLE 338-8 TREATMENT GOALS FOR ADULTS WITH DIABETES[a]

Index	Goal
Glycemic control[b]	
A1C	<7.0[c]
Preprandial capillary plasma glucose	5.0–7.2 mmol/L (90–130 mg/dL)
Peak postprandial capillary plasma glucose	<10.0 mmol/L (<180 mg/dL)[d]
Blood pressure	<130/80[e]
Lipids[f]	
Low-density lipoprotein	<2.6 mmol/L (<100 mg/dL)
High-density lipoprotein	>1.1 mmol/L (>40 mg/dL)[g]
Triglycerides	<1.7 mmol/L (<150 mg/dL)

[a]As recommended by the ADA; Goals should be developed for each patient (see text). Goals may be different for certain patient populations.
[b]A1C is primary goal.
[c]While the ADA recommends an A1C < 7.0% in general, in the individual patient it recommends an "... A1C as close to normal (<6.0%) as possible without significant hypoglycemia...." Normal range for A1C—4.0–6.0 (DCCT-based assay).
[d]One-two hours after beginning of a meal.
[e]In patients with reduced GFR and macroalbuminuria, the goal is <125/75.
[f]In decreasing order of priority.
[g]For women, some suggest a goal that is 0.25 mmol/L (10 mg/dL) higher.
Source: Adapted from American Diabetes Association, 2007.

A number of names are sometimes applied to different approaches to diabetes care, such as intensive insulin therapy, intensive glycemic control, and "tight control." The current chapter, however, will use the term *comprehensive diabetes care* to emphasize the fact that optimal diabetes therapy involves more than plasma glucose management. Though glycemic control is central to optimal diabetes therapy, comprehensive diabetes care of both type 1 and type 2 DM should also detect and manage DM-specific complications and modify risk factors for DM-associated diseases. In addition to the physical aspects of DM, social, family, financial, cultural, and employment-related issues may impact diabetes care. The International Diabetes Federation (IDF), recognizing that resources available for diabetes care varies widely throughout the world, has issued guidelines for standard care (a well-developed service base and with health care funding systems consuming a significant part of their national wealth), minimal care (health care settings with very limited resources), and comprehensive care (health care settings with considerable resources). This chapter provides guidance for this comprehensive level of diabetes care.

PATIENT EDUCATION ABOUT DM, NUTRITION, AND EXERCISE

The patient with type 1 or type 2 DM should receive education about nutrition, exercise, care of diabetes during illness, and medications to lower the plasma glucose. Along with improved compliance, patient education allows individuals with DM to assume greater responsibility for their care. Patient education should be viewed as a continuing process with regular visits for reinforcement; it should not be a process that is completed after one or two visits to a nurse educator or nutritionist. The ADA refers to education about the individualized management plan for the patient as diabetes self-management education (DSME). More frequent contact between the patient and the diabetes management team (electronic, telephone, etc.) improves glycemic control.

Diabetes Education The diabetes educator is a health care professional (nurse, dietician, or pharmacist) with specialized patient education skills who is certified in diabetes education (e.g., American Association of Diabetes Educators). Education topics important for optimal diabetes care include self-monitoring of blood glucose; urine ketone monitoring (type 1 DM); insulin administration; guidelines for diabetes management during illnesses; management of hypoglycemia; foot and skin care; diabetes management before, during, and after exercise; and risk factor–modifying activities.

Nutrition *Medical nutrition therapy* (MNT) is a term used by the ADA to describe the optimal coordination of caloric intake with other aspects of diabetes therapy (insulin, exercise, weight loss). The ADA has issued recommendations for three types of MNT. Primary prevention measures of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with pre-diabetes) by promoting weight reduction. Medical treatment of obesity is a rapidly evolving area and is discussed in Chap. 75. Secondary prevention measures of MNT are directed at preventing or delaying diabetes-related complications in diabetic individuals by improving glycemic control. Tertiary prevention measures of MNT are directed at managing diabetes-related complications (cardiovascular disease, nephropathy) in diabetic individuals. For example, in individuals with diabetes and chronic kidney disease, protein intake should be limited to 0.8 g/kg of body weight per day. MNT in patients with diabetes and cardiovascular disease should incorporate dietary principles used in non-diabetic patients with cardiovascular disease. While the recommendations for all three types of MNT overlap; this chapter emphasizes secondary prevention measures of MNT. Pharmacologic approaches that facilitate weight loss and bariatric surgery should be considered in selected patients (Chap. 75).

As for the general population, a diet that includes fruits, vegetables, fiber-containing foods, and low-fat milk is advised. Like other aspects of DM therapy, MNT must be adjusted to meet the goals of the indi-

TABLE 338-9 NUTRITIONAL RECOMMENDATIONS FOR ADULTS WITH DIABETES[a]

Fat
20–35% of total caloric intake
Saturated fat < 7% of total calories
<200 mg/day of dietary cholesterol
Two or more servings of fish/week provide ω-3 polyunsaturated fatty acids
Minimal trans fat consumption
Carbohydrate
45–65% of total caloric intake (low-carbohydrate diets are not recommended)
Amount and type of carbohydrate important[b]
Sucrose-containing foods may be consumed with adjustments in insulin dose
Protein
10–35% of total caloric intake (high-protein diets are not recommended)
Other components
Fiber-containing foods may reduce postprandial glucose excursions
Nonnutrient sweeteners

[a]See text for differences for patients with type 1 or type 2 diabetes. As for the general population, a healthy diet includes fruits, vegetables, and fiber-containing foods.
[b]Amount of carbohydrate determined by estimating grams of carbohydrate in diet; glycemic index reflects how consumption of a particular food affects the blood glucose.
Source: Adapted from American Diabetes Association, 2007.

vidual patient. Furthermore, MNT education is an important component of comprehensive diabetes care and should be reinforced by regular patient education. In general, the components of optimal MNT are similar for individuals with type 1 or type 2 DM (Table 338-9). Historically, nutrition education imposed restrictive, complicated regimens on the patient. Current practices have greatly changed, though many patients and health care providers still view the diabetic diet as monolithic and static. For example, MNT now includes foods with sucrose and seeks to modify other risk factors such as hyperlipidemia and hypertension rather than focusing exclusively on weight loss in individuals with type 2 DM. The *glycemic index* is an estimate of the postprandial rise in the blood glucose when a certain amount of that food is consumed. Consumption of foods with a low glycemic index appears to reduce postprandial glucose excursions and improve glycemic control. Reduced calorie and nonnutritive sweeteners are useful. Currently, evidence does not support supplementation of the diet with vitamins, antioxidants (vitamin C and E), or micronutrients (chromium) in patients with diabetes. The goal of MNT in the individual with type 1 DM is to coordinate and match the caloric intake, both temporally and quantitatively, with the appropriate amount of insulin. MNT in type 1 DM and self-monitoring of blood glucose must be integrated to define the optimal insulin regimen. The ADA encourages patients and providers to utilize carbohydrate counting or exchange systems to estimate the nutrient content of a meal or snack. Based on the patient's estimate of the carbohydrate content of meal, an insulin-to-carbohydrate ratio determines the bolus insulin dose for a meal or snack. MNT must be flexible enough to allow for exercise, and the insulin regimen must allow for deviations in caloric intake. An important component of MNT in type 1 DM is to minimize the weight gain often associated with intensive diabetes management.

The goals of MNT in type 2 DM are slightly different and address the greatly increased prevalence of cardiovascular risk factors (hypertension, dyslipidemia, obesity) and disease in this population. The majority of these individuals are obese, and weight loss is strongly encouraged and should remain an important goal. Hypocaloric diets and modest weight loss (5–7%) often result in rapid and dramatic glucose lowering in individuals with new-onset type 2 DM. Nevertheless, numerous studies document that long-term weight loss is uncommon. MNT for type 2 DM should emphasize modest caloric reduction, reduced fat intake, increased physical activity, and reduction of hyperlipidemia and hypertension. Increased consumption of soluble, dietary fiber may improve glycemic control in individuals with type 2 DM. Weight loss and exercise improve insulin resistance.

Exercise Exercise has multiple positive benefits including cardiovascular risk reduction, reduced blood pressure, maintenance of muscle mass, reduction in body fat, and weight loss. For individuals with type 1 or type 2 DM, exercise is also useful for lowering plasma glucose (during and following exercise) and increasing insulin sensitivity. In patients with diabetes, the ADA recommends 150 min/week (distributed over at least 3 days) of aerobic physical activity. In patients with type 2 DM, the exercise regimen should also include resistance training.

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

To avoid exercise-related hyper- or hypoglycemia, individuals with type 1 DM should: (1) monitor blood glucose before, during, and after exercise; (2) delay exercise if blood glucose is >14 mmol/L (250 mg/dL) and ketones are present; (3) if the blood glucose is <5.6 mmol/L (100 mg/dL), ingest carbohydrate before exercising; (3) monitor glucose during exercise and ingest carbohydrate to prevent hypoglycemia; (4) decrease insulin doses (based on previous experience) before exercise and inject insulin into a nonexercising area; and (5) learn individual glucose responses to different types of exercise and increase food intake for up to 24 h after exercise, depending on intensity and duration of exercise. In individuals with type 2 DM, exercise-related hypoglycemia is less common but can occur in individuals taking either insulin or insulin secretagogues.

Because asymptomatic cardiovascular disease appears at a younger age in both type 1 and type 2 DM, formal exercise tolerance testing may be warranted in diabetic individuals with any of the following: age >35 years, diabetes duration >15 years (type 1 DM) or >10 years (type 2 DM), microvascular complications of DM (retinopathy, microalbuminuria, or nephropathy), PAD, other risk factors of CAD, or autonomic neuropathy. Untreated proliferative retinopathy is a relative contraindication to vigorous exercise, as this may lead to vitreous hemorrhage or retinal detachment.

MONITORING THE LEVEL OF GLYCEMIC CONTROL

Optimal monitoring of glycemic control involves plasma glucose measurements by the patient and an assessment of long-term control by the physician (measurement of hemoglobin A1C and review of the patient's self-measurements of plasma glucose). These measurements are complementary: the patient's measurements provide a picture of short-term glycemic control, whereas the A1C reflects average glycemic control over the previous 2–3 months.

Self-Monitoring of Blood Glucose Self-monitoring of blood glucose (SMBG) is the standard of care in diabetes management and allows the patient to monitor his or her blood glucose at any time. In SMBG, a small drop of blood and an easily detectable enzymatic reaction allow measurement of the capillary plasma glucose. Many glucose monitors can rapidly and accurately measure glucose (calibrated to provide plasma glucose value even though blood glucose is measured) in small amounts of blood (3–10 μl) obtained from the fingertip; alternative testing sites (e.g., forearm) are less reliable, especially when the blood glucose is changing rapidly (postprandially). A large number of blood glucose monitors are available, and the certified diabetes educator is critical in helping the patient select the optimal device and learn to use it properly. By combining glucose measurements with diet history,

medication changes, and exercise history, the physician and patient can improve the treatment program.

The frequency of SMBG measurements must be individualized and adapted to address the goals of diabetes care. Individuals with type 1 DM or individuals with type 2 DM taking multiple insulin injections each day should routinely measure their plasma glucose three or more times per day to estimate and select mealtime boluses of short-acting insulin and to modify long-acting insulin doses. Most individuals with type 2 DM require less frequent monitoring, though the optimal frequency of SMBG has not been clearly defined. Individuals with type 2 DM who are taking insulin should utilize SMBG more frequently than those on oral agents. Individuals with type 2 DM who are on oral medications should utilize SMBG as a means of assessing the efficacy of their medication and the impact of diet. Since plasma glucose levels fluctuate less in these individuals, one to two SMBG measurements per day (or fewer in patients who are on oral agents or are diet-controlled) may be sufficient. Most measurements in individuals with type 1 or type 2 DM should be performed prior to a meal and supplemented with postprandial measurements to assist in reaching postprandial glucose targets (Table 338-8). Urine glucose testing does not provide an accurate assessment of glycemic control.

Devices for continuous blood glucose monitoring are the subject of intense investigation, as some systems have been approved by the FDA and others are in various stages of development. Currently, the use of these devices in routine diabetes management is limited, and they do not replace the need for a traditional glucose meter. This rapidly evolving technology requires substantial expertise on the part of the diabetes management team and the patient. Current continuous glucose monitoring systems (CGMS) measure the glucose in interstitial fluid that is in equilibrium with the blood glucose. Alarms notify the patient if the blood glucose falls into the hypoglycemic range. The FDA refers to these as "minimally invasive" or "noninvasive" depending on how the interstitial fluid is obtained. Several devices use an indwelling subcutaneous catheter to monitor interstitial fluid glucose and provide either real time or retrospective glucose values. Although clinical experience with these devices is limited, they appear to provide useful short-term information about the patterns of glucose changes as well as an enhanced ability to detect hypoglycemic episodes.

Ketones are an indicator of early diabetic ketoacidosis and should be measured in individuals with type 1 DM when the plasma glucose is consistently >16.7 mmol/L (300 mg/dL); during a concurrent illness; or with symptoms such as nausea, vomiting, or abdominal pain. Blood measurement of β-hydroxybutyrate is preferred over urine testing with nitroprusside-based assays that measure only acetoacetate and acetone.

Assessment of Long-Term Glycemic Control Measurement of glycated hemoglobin is the standard method for assessing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemoglobin; this alteration reflects the glycemic history over the previous 2–3 months, since erythrocytes have an average life span of 120 days (glycemic level in the preceding month contributes about 50% to the A1C value). There are numerous laboratory methods for measuring the various forms of glycated hemoglobin, and these have significant interassay variations. Since glycated hemoglobin measurements are usually compared to prior measurements, it is essential for the assay results to be comparable. Depending on the assay methodology, hemoglobinopathies, anemias, reticulocytosis, transfusions, and uremia may interfere with the A1C result. Measurement of A1C at the "point of care" allows for more rapid feedback and may therefore assist in adjustment of therapy.

Glycated hemoglobin or A1C should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. As the primary predictor of long-term complications of DM, the A1C should mirror, to a certain extent, the short-term measurements of SMBG. These two measurements are complementary in that recent intercurrent illnesses may impact the SMBG measurements but not the A1C. Likewise, postprandial and nocturnal hyperglycemia may not be detected by the SMBG of fasting and preprandial capillary plasma glucose but will be reflected in the A1C. In standardized assays, the A1C approximates the following mean plasma glucose values: an A1C of 6% is 7.5 mmol/L (135 mg/dL), 7% is 9.5 mmol/L (170 mg/dL), 8% is 11.5 mmol/L (205 mg/dL), etc. [A 1% rise in the A1C translates into a 2.0-mmol/L (35 mg/dL) increase in the mean glucose.] In patients achieving their glycemic goal, the ADA recommends measurement of the A1C at least twice per year. More frequent testing (every 3 months) is warranted when glycemic control is inadequate, when therapy has changed, or in most patients with type 1 DM. The degree of glycation of other proteins, such as albumin, can be used as an alternative indicator of glycemic control when the A1C is inaccurate (hemolytic anemia, hemoglobinopathies). The fructosamine assay (measuring glycated albumin) reflects the glycemic status over the prior 2 weeks. Alternative assays of glycemic control (including the 1,5 anhydroglucitol assay) should not be routinely used since studies demonstrating that it accurately predicts the complications of DM are lacking.

Rx TYPE 1 AND TYPE 2 DIABETES MELLITUS

ESTABLISHMENT OF TARGET LEVEL OF GLYCEMIC CONTROL

Because the complications of DM are related to glycemic control, normoglycemia or near normoglycemia is the desired, but often elusive, goal for most patients. However, normalization of the plasma glucose for long periods of time is extremely difficult, as demonstrated by the DCCT. Regardless of the level of hyperglycemia, improvement in glycemic control will lower the risk of diabetes complications (Fig. 338-8).

The target for glycemic control (as reflected by the A1C) must be individualized, and the goals of therapy should be developed in consultation with the patient after considering a number of medical, social, and lifestyle issues. Some important factors to consider include the patient's age, ability to understand and implement a complex treatment regimen, presence and severity of complications of diabetes, ability to recognize hypoglycemic symptoms, presence of other medical conditions or treatments that might alter the response to therapy, lifestyle and occupation (e.g., possible consequences of experiencing hypoglycemia on the job), and level of support available from family and friends.

The ADA suggests that the glycemic goal is to achieve an A1C as close to normal as possible without significant hypoglycemia. In general, the target A1C should be <7.0% (Table 338-8) with a more stringent target (<6%) for many patients. A higher A1C goal may be appropriate for the very young or old or in individuals with limited life span or comorbid conditions. The major consideration is the frequency and severity of hypoglycemia, since this becomes more common with a more stringent A1C goal. Other groups (International Diabetes Federation and American Association of Clinical Endocrinology) have suggested that the A1C goal should be ≤6.5% in most individuals, based primarily on the observation that there is no lower limit of A1C in terms of reducing diabetes-specific complications.

TYPE 1 DIABETES MELLITUS **General Aspects** The ADA recommendations for fasting and bedtime glycemic goals and A1C targets are summarized in Table 338-8. The goal is to design and implement insulin regimens that mimic physiologic insulin secretion. Because individuals with type 1 DM partially or completely lack endogenous insulin production, administration of basal, exogenous insulin is essential for regulating glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis. Likewise, insulin replacement for meals should be appropriate for the carbohydrate intake and promote normal glucose utilization and storage.

Intensive Management Intensive diabetes management has the goal of achieving euglycemia or near-normal glycemia. This approach requires multiple resources including thorough and continuing patient education, comprehensive recording of plasma glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches glucose intake and insulin dose. Insulin regimens usually include multiple-component insulin regimens, multiple daily injections (MDI), or insulin infusion devices (each discussed below).

The benefits of intensive diabetes management and improved glycemic control include a reduction in the microvascular complications of DM and a reduction in the macrovascular complications of DM, which persists after a period of near-normoglycemia. From a psychological standpoint, the pa-

nt experiences greater control over his or her di-
tes and often notes an improved sense of well-
ng, greater flexibility in the timing and content
meals, and the capability to alter insulin dosing
h exercise. In addition, intensive diabetes man-
ement in pregnancy reduces the risk of fetal
formations and morbidity. Intensive diabetes
nagement is strongly encouraged in newly di-
nosed patients with type 1 DM because it may
long the period of C-peptide production,
ich may result in better glycemic control and a
duced risk of serious hypoglycemia.

Although intensive management confers im-
ressive benefits, it is also accompanied by signifi-
ant personal and financial costs and is therefore
ot appropriate for all individuals.

TABLE 338-10 PHARMACOKINETICS OF INSULIN PREPARATIONS

Preparation	Time of Action		
	Onset, h	Peak, h	Effective Duration, h
Short-acting, subcutaneous			
Lispro	<0.25	0.5–1.5	3–4
Aspart	<0.25	0.5–1.5	3–4
Glulisine	<0.25	0.5–1.5	3–4
Regular	0.5–1.0	2–3	4–6
Short-acting, inhaled			
Inhaled regular insulin	<0.25	0.5–1.5	4–6
Long-acting			
NPH	1–4	6–10	10–16
Detemir	1–4	—[a]	12–20
Glargine	1–4	—[a]	24
Insulin Combinations			
75/25–75% protamine lispro, 25% lispro	<0.25	1.5 h[b]	Up to 10–16
70/30–70% protamine aspart, 30% aspart	<0.25	1.5 h[b]	Up to 10–16
50/50–50% protamine lispro, 50% lispro	<0.25	1.5 h[b]	Up to 10–16
70/30–70% NPH, 30% regular insulin	0.5–1	Dual	10–16
50/50–50% NPH, 50% regular insulin	0.5–1	Dual	10–16

[a]Glargine has minimal peak activity; detemir has some peak activity at 6–14 h.
[b]Dual: two peaks; one at 2–3 h; the second several hours later.
Source: Adapted from JS Skyler, *Therapy for Diabetes Mellitus and Related Disorders*, American Diabetes Association, Alexandria, VA, 2004.

nsulin Preparations Current insulin prepara-
ions are generated by recombinant DNA technol-
gy and consist of the amino acid sequence of
human insulin or variations thereof. Animal insulin
(beef or pork) is no longer used. In the United
States, most insulin is formulated as U-100 (100
units/mL), whereas in some other countries it is
available in other concentrations (e.g., U-40 = 40
units/mL). Human insulin has been formulated
with distinctive pharmacokinetics or genetically
modified to more closely mimic physiologic insulin secretion. Insulins can be classified as short-acting or long-acting **(Table 338-10)**. For example, one short-acting insulin formulation, insulin lispro, is an insulin analogue in which the 28th and 29th amino acids (lysine and proline) on the insulin B chain have been reversed by recombinant DNA technology. Insulin aspart and insulin glulisine are other genetically modified insulin analogues with properties similar to lispro. These insulin analogues have full biologic activity but less tendency for self aggregation, resulting in more rapid absorption and onset of action and a shorter duration of action. These characteristics are particularly advantageous for allowing entrainment of insulin injection and action to rising plasma glucose levels following meals. The shorter duration of action also appears to be associated with a decreased number of hypoglycemic episodes, primarily because the decay of insulin action corresponds to the decline in plasma glucose after a meal. Thus, insulin aspart, lispro, or glulisine is preferred over regular insulin for prandial coverage. Insulin glargine is a long-acting biosynthetic human insulin that differs from normal insulin in that asparagine is replaced by glycine at amino acid 21, and two arginine residues are added to the C-terminus of the B chain. Compared to NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is no pronounced peak. A lower incidence of hypoglycemia, especially at night, has been reported with insulin glargine when compared to NPH insulin. Insulin detemir has a fatty acid side chain that prolongs its action by slowing absorption and catabolism. Regular and NPH insulin have the native insulin amino acid sequence. Regular insulin formulated as U-500 (500 units/mL) is available and sometimes useful in severely insulin resistant patients.

Basal insulin requirements are provided by long-acting (NPH insulin, insulin glargine, or insulin detemir) insulin formulations. These are usually prescribed with short-acting insulin in an attempt to mimic physiologic insulin release with meals. Although mixing of NPH and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially the short-acting insulins). For example, lispro absorption is delayed by mixing with NPH. The alteration in insulin absorption when the patient mixes different insulin formulations should not discourage mixing insulins. However, the following guidelines should be followed: (1) mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing); (2) do not store insulin as a mixture; (3) follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin; and (4) do not mix insulin glargine or detemir with other insulins. The miscibility of human regular and NPH insulin allows for the production of combination insulins that contain 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular (50/50). Other combination insulin formulations are insulin aspart (70/30) and insulin lispro (75/25 and 50/50). By including some insulin analogue mixed with protamine, these combinations have a short-acting and long-acting profile (Table 338-10). While more convenient for the patient (only two injections/day), combination insulin formulations do not allow independent adjustment of short-acting and long-acting activity. Several insulin formulations are available as insulin "pens," which may be more convenient for some patients.

Insulin can also be delivered by inhalation by using a powder formulation of regular insulin and a delivery device. For insulin delivery, the patient uses a powdered formulation of insulin (a "blister") and a specialized inhaler to release a cloud of insulin into a reservoir from which the aerosolized insulin is inhaled. Inhaled insulin is short-acting, with an onset of action similar to insulin analogues but with a duration of action similar to regular insulin. It is therefore used for prandial coverage. Inhaled insulin must either be combined with an injected long-acting insulin to provide basal insulin coverage in type 1 or type 2 DM (Table 338-10) or used in combination with oral agents in patients with type 2 DM. Inhaled insulin appears to be similar to injected regular insulin in terms of glycemic control. It is available in 1- and 3-mg "blisters," which are equivalent to 3 and 8 units of injected regular insulin. To deliver a larger dose requires the use of more than one blister. Inhaled insulin is not approved for use in patients who smoke or have chronic lung diseases. Pulmonary function testing should be performed before starting inhaled insulin and repeated after 6 months of treatment and then annually. Side effects include cough, which improves with continued use, and hypoglycemia in a frequency similar to that seen with injected regular insulin. Long-term safety of inhaled insulin is not known. Proper use of the inhalation device requires patient education. Inhaled insulin has no physiologic advantage over injected short-acting insulin but may be considered in selected patients with type 2 DM who are unwilling to use injected insulin. Other inhaled insulin formulations are under development.

Insulin Regimens Representations of the various insulin regimens that may be utilized in type 1 DM are illustrated in **Fig. 338-13**. Although the insulin profiles are depicted as "smooth," symmetric curves, there is considerable patient-to-patient variation in the peak and duration. In all regimens, long-acting insulins (NPH, glargine, or detemir) supply basal insulin, whereas regular, insulin aspart, glulisine, or lispro insulin provides prandial insulin. Short-acting insulin analogues should be injected just before (<20 min) or just after a meal; regular insulin is given 30–45 min prior to a meal.

A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous insulin is secreted into the portal venous system. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels. No insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet. However, the most physiologic regimens entail more frequent insulin injections, greater reliance on short-acting insulin, and more frequent capillary plas-

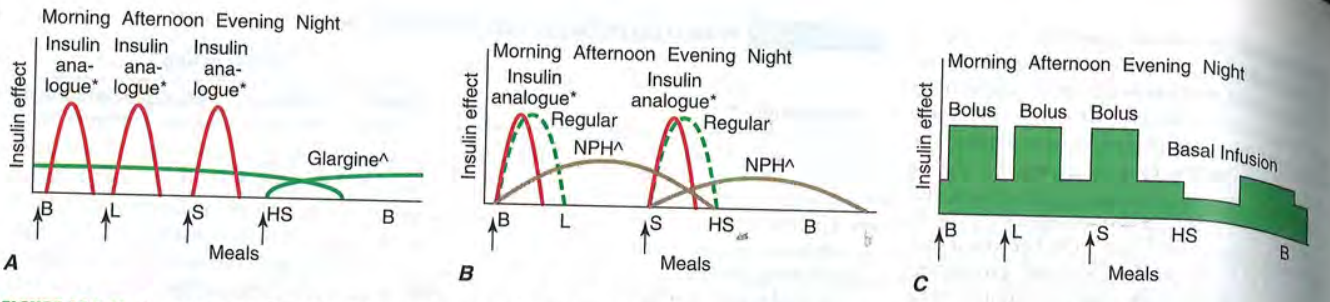


FIGURE 338-13 Representative insulin regimens for the treatment of diabetes. For each panel, the *y*-axis shows the amount of insulin effect and the *x*-axis shows the time of day. B, breakfast; L, lunch; S, supper; HS, bedtime; CSII, continuous subcutaneous insulin infusion. *Lispro, glulisine, or insulin aspart can be used. The time of insulin injection is shown with a vertical arrow. The type of insulin is noted above each insulin curve. ***A.*** A multiple-component insulin regimen consisting of long-acting insulin (^, one shot of glargine or two shots of detemir) to provide basal insulin coverage and three shots of glulisine, lispro, or insulin aspart to provide glycemic coverage for each meal. ***B.*** The injection of two shots of long-acting insulin (^, NPH or detemir) and short-acting insulin [glulisine, lispro, insulin aspart (solid red line), or regular (green dashed line)]. Only one formulation of short-acting insulin is used. ***C.*** Insulin administration by insulin infusion device is shown with the basal insulin and a bolus injection at each meal. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Glulisine, lispro, or insulin aspart is used in the insulin pump. *[Adapted from H Lebovitz (ed): Therapy for Diabetes Mellitus. American Diabetes Association, Alexandria, VA, 2004.]*

ma glucose measurements. In general, individuals with type 1 DM require 0.5–1.0 U/kg per day of insulin divided into multiple doses, with ~50% of the insulin given as basal insulin.

Multiple-component insulin regimens refer to the combination of basal insulin and bolus insulin (preprandial short-acting insulin). The timing and dose of short-acting, preprandial insulin are altered to accommodate the SMBG results, anticipated food intake, and physical activity. Such regimens offer the patient with type 1 diabetes more flexibility in terms of lifestyle and the best chance for achieving near normoglycemia. One such regimen, shown in Fig. 338-13*B*, consists of basal insulin with glargine or detemir and preprandial lispro, glulisine, or insulin aspart. The insulin aspart, glulisine, or lispro dose is based on individualized algorithms that integrate the preprandial glucose and the anticipated carbohydrate intake. To determine the meal component of the preprandial insulin dose, the patient uses an insulin:carbohydrate ratio (a common ratio is 1–1.5 units/10 g of carbohydrate, but this must be determined for each individual). To this insulin dose is added the supplemental or correcting insulin based on the preprandial blood glucose [one formula uses 1 unit of insulin for every 2.7 mmol/L (50 mg/dL) over the preprandial glucose target; another formula uses (body weight in kg) × (blood glucose – desired glucose in mg/dL)/1500]. An alternative multiple-component insulin regimen consists of bedtime NPH insulin, a small dose of NPH insulin at breakfast (20–30% of bedtime dose), and preprandial short-acting insulin. Other variations of this regimen are in use but have the disadvantage that NPH has a significant peak, making hypoglycemia more common. Frequent SMBG (>3 times per day) is absolutely essential for all types of insulin regimens.

One commonly used regimen consists of twice-daily injections of a long-acting insulin like NPH (detemir could be used instead) mixed with a short-acting insulin before the morning and evening meal (Fig. 338-13*A*). Such regimens usually prescribe two-thirds of the total daily insulin dose in the morning (with about two-thirds given as long-acting insulin and one-third as short-acting) and one-third before the evening meal (with approximately one-half given as long-acting insulin and one-half as short-acting). The drawback to such a regimen is that it enforces a rigid schedule on the patient, in terms of daily activity and the content and timing of meals. Although it is simple and effective at avoiding severe hyperglycemia, it does not generate near-normal glycemic control in most individuals with type 1 DM. Moreover, if the patient's meal pattern or content varies or if physical activity is increased, hyperglycemia or hypoglycemia may result. Moving the long-acting insulin from before the evening meal to bedtime may avoid nocturnal hypoglycemia and provide more insulin as glucose levels rise in the early morning (so-called dawn phenomenon). The insulin dose in such regimens should be adjusted based on SMBG results with the following general assumptions: (1) the fasting glucose is primarily determined by the prior evening long-acting insulin; (2) the pre-lunch glucose is a function of the morning short-acting insulin; (3) the pre-supper glucose is a function of the morning long-acting insulin; and (4) the bedtime glucose is a function of the pre-supper, short-acting insulin. This is not an optimal regimen for the patient with type 1 DM, but is sometimes used for patients with type 2 diabetes.

Continuous subcutaneous insulin infusion (CSII) is a very effective insulin regimen for the patient with type 1 diabetes (Fig. 338-13*C*). To the basal insulin infusion, a preprandial insulin ("bolus") is delivered by the insulin infusion device based on instructions from the patient, who uses an individualized algorithm incorporating the preprandial plasma glucose and anticipated carbohydrate intake (see above). These sophisticated insulin infusion devices can accurately deliver small doses of insulin (microliters per hour) and have several advantages: (1) multiple basal infusion rates can be programmed to accommodate nocturnal versus daytime basal insulin requirement, (2) basal infusion rates can be altered during periods of exercise, (3) different waveforms of insulin infusion with meal-related bolus allow better matching of insulin depending on meal composition, and (4) programmed algorithms consider prior insulin administration and blood glucose values in calculating the insulin dose. These devices require a health professional with considerable experience with insulin infusion devices and very frequent patient interactions with the diabetes management team. Insulin infusion devices present unique challenges, such as infection at the infusion site, unexplained hyperglycemia because the infusion set becomes obstructed, or diabetic ketoacidosis if the pump becomes disconnected. Since most physicians use lispro, glulisine, or insulin aspart in CSII, the extremely short half-life of these insulins quickly lead to insulin deficiency if the delivery system is interrupted. Essential to the safe use of infusion devices is thorough patient education about pump function and frequent SMBG. Efforts to create a closed loop system in which data from continuous glucose measurement regulates the insulin infusion rate continue.

Other Agents That Improve Glucose Control The role of amylin, a 37-amino-acid peptide cosecreted with insulin from pancreatic beta cells, in normal glucose homeostasis is uncertain. However, based on the rationale that patients who are insulin deficient are also amylin deficient, an analogue of amylin (pramlintide) was created and found to reduce postprandial glycemic excursions in type 1 and type 2 diabetic patients taking insulin. Pramlintide injected just before a meal slows gastric emptying and suppresses glucagon but does not alter insulin levels. Pramlintide is approved for insulin-treated patients with type 1 and type 2 DM. Addition of pramlintide produces a modest reduction in the A1C and seems to dampen meal-related glucose excursions. In type 1 diabetes, pramlintide is started as a 15-μg SC injection before each meal and titrated up to a maximum of 30–60 μg as tolerated. In type 2 DM, pramlintide is started as a 60-μg SC injection before each meal and may be titrated up to a maximum of 120 μg. The major side effects are nausea and vomiting, and dose escalations should be slow to limit these side effects. Because pramlintide slows gastric emptying, it may influence absorption of other medications and should not be used in combination with other drugs that slow GI motility. The short-acting insulin given before the meal should initially be reduced to avoid hypoglycemia and then titrated as the effects of the pramlintide

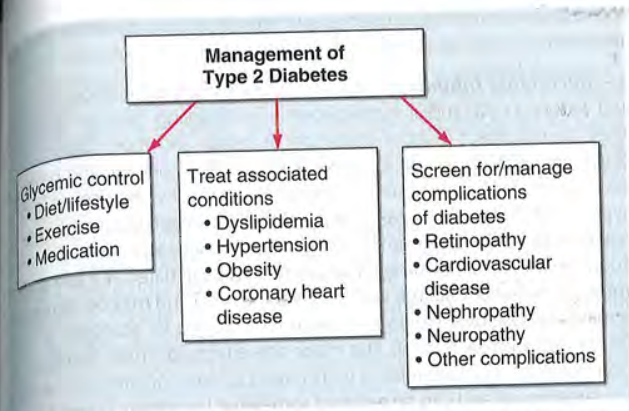


FIGURE 338-14 Essential elements in comprehensive diabetes care of type 2 diabetes.

become evident. α-Glucosidase inhibitors are another type of agent that may be used in patients with type 1 DM (see below).

TYPE 2 DIABETES MELLITUS **General Aspects** The goals of therapy for type 2 DM are similar to those in type 1. While glycemic control tends to dominate the management of type 1 DM, the care of individuals with type 2 DM must also include attention to the treatment of conditions associated with type 2 DM (obesity, hypertension, dyslipidemia, cardiovascular disease) and detection/management of DM-related complications (Fig. 338-14). DM-specific complications may be present in up to 20–50% of individuals with newly diagnosed type 2 DM. Reduction in cardiovascular risk is of paramount importance as this is the leading cause of mortality in these individuals. Efforts to achieve blood pressure and lipid goals (Table 338-8) should begin in concert with glucose-lowering interventions.

Type 2 diabetes management should begin with MNT (discussed above). An exercise regimen to increase insulin sensitivity and promote weight loss should also be instituted. Pharmacologic approaches to the management of type 2 DM include oral glucose-lowering agents, insulin, and other agents that improve glucose control; most physicians and patients prefer oral glucose-lowering agents as the initial choice (discussed below after review of various medications). Any therapy that improves glycemic control reduces "glucose toxicity" to the islet cells and improves endogenous insulin secretion. However, type 2 DM is a progressive disorder and ultimately requires multiple therapeutic agents and often insulin.

Glucose-Lowering Agents Advances in the therapy of type 2 DM have generated considerable enthusiasm for oral glucose-lowering agents that target different pathophysiologic processes in type 2 DM. Based on their mechanisms of action, glucose-lowering agents are subdivided into agents that increase insulin secretion, reduce glucose production, increase insulin sensitivity, and enhance GLP-1 action (Table 338-11). Glucose-lowering agents (with the exception of α-glucosidase inhibitors and an amylin analogue) are ineffective in type 1 DM and should not be used for glucose management of severely ill individuals with type 2 DM. Insulin is sometimes the initial glucose-lowering agent.

Insulin Secretagogues Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell (Fig. 338-4). These drugs are most effective in individuals with type 2 DM of relatively recent onset (<5 years), who have residual endogenous insulin production. At maximum doses, first-generation sulfonylureas are similar in potency to second-generation agents but have a longer half-life,

TABLE 383-11 GLUCOSE-LOWERING THERAPIES FOR TYPE 2 DIABETES

	Mechanism of Action	Examples	A1C Reduction (%)[a]	Agent-Specific Advantages	Agent-Specific Disadvantages	Contraindications/ Relative Contraindications
Oral						
Biguanides	↓ Hepatic glucose production, weight loss, glucose, utilization, insulin resistance	Metformin	1–2	Weight loss	Lactic acidosis, diarrhea, nausea	Serum creatinine >1.5 mg/dL (men) >1.4 mg/dL (women), CHF, radiographic contrast studies, seriously ill patients, acidosis
α-Glucosidase inhibitors	↓ Glucose absorption	Acarbose, Miglitol	0.5–0.8	Reduce postprandial glycemia	GI flatulence, liver function tests	Renal/liver disease
Dipeptidyl peptidase IV inhibitors	Prolong endogenous GLP-1 action	Sitagliptin	0.5–1.0	Does not cause hypoglycemia		Reduce dose with renal disease
Insulin secretagogues—sulfonylureas	↑ Insulin secretion	Table 338-12	1–2	Lower fasting blood glucose	Hypoglycemia, weight gain	Renal/liver disease
Insulin secretagogues—nonsulfonylureas	↑ Insulin secretion	Table 338-12	1–2	Short onset of action, lowers postprandial glucose	Hypoglycemia	Renal/liver disease
Thiazolidinediones	↓ Insulin resistance, ↑ glucose utilization	Rosiglitazone, Pioglitazone	0.5–1.4	Lower insulin requirements	Peripheral edema, CHF, weight gain, fractures, macular edema; rosiglitazone may increase risk of MI	Congestive heart failure, liver disease
Parenteral						
Insulin	↑ Glucose utilization and other anabolic actions	Table 323-11	No limit	Known safety profile	Injection, weight gain, hypoglycemia	
GLP-1 agonist	↑ Insulin, ↓ Glucagon, slow gastric emptying	Exenatide	0.5–1.0	Weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin secretagogues	Renal disease, agents that also slow GI motility
Amylin agonist[b]	Slow gastric emptying, ↓ Glucagon	Pramlintide	0.25–0.5	Reduce postprandial glycemia, weight loss	Injection, nausea, ↑ risk of hypoglycemia with insulin	Agents that also slow GI motility
Medical nutrition therapy and physical activity	↓ Insulin, resistance, ↑ insulin secretion	Low-calorie, low-fat diet, exercise	1–2	Other health benefits	Compliance difficult, long-term success low	

[a]A1C reduction depends partly on starting A1C.
[b]Amylin agonist is approved for use in type 1 and type 2 diabetes.

TABLE 338-12 CHARACTERISTICS OF ORAL AGENTS THAT INCREASE INSULIN SECRETION

Generic Name	Approved Daily Dosage Range, mg	Duration of Action, h
Sulfonylurea—first generation		
Chlorpropamide	100–500	>48
Tolazamide	100–1000	12–24
Tolbutamide	500–3000	6–12
Sulfonylurea—second generation		
Glimepiride	1–8	24
Glipizide	2.5–40	12–18
Glipizide (extended release)	5–10	24
Glyburide	1.25–20	12–24
Glyburide (micronized)	0.75–12	12–24
Nonsulfonylureas		
Repaglinide	0.5–16	2–6
Nateglinide	180–360	2–4

Source: Adapted from BR Zimmerman (ed): *Medical Management of Type 2 Diabetes*, 4th ed. American Diabetes Association, Alexandria, VA, 1998.

a greater incidence of hypoglycemia, and more frequent drug interactions **(Table 338-12)**. Thus, second-generation sulfonylureas are generally preferred. An advantage to a more rapid onset of action is better coverage of the postprandial glucose rise, but the shorter half-life of such agents requires more than once-a-day dosing. Sulfonylureas reduce both fasting and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on SMBG. In general, sulfonylureas increase insulin acutely and thus should be taken shortly before a meal; with chronic therapy, though, the insulin release is more sustained. Glimepiride and glipizide can be given in a single daily dose and are preferred over glyburide. Repaglinide and nateglinide are not sulfonylureas but also interact with the ATP-sensitive potassium channel. Because of their short half-life, these agents are given with each meal or immediately before to reduce meal-related glucose excursions.

Insulin secretagogues are generally well tolerated. All of these agents, however, have the potential to cause profound and persistent hypoglycemia, especially in elderly individuals. Hypoglycemia is usually related to delayed meals, increased physical activity, alcohol intake, or renal insufficiency. Individuals who ingest an overdose of some agents develop prolonged and serious hypoglycemia and should be monitored closely in the hospital (Chap. 339). Most sulfonylureas are metabolized in the liver to compounds (some of which are active) that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable. Weight gain, a common side effect of sulfonylurea therapy, results from the increased insulin levels and improvement in glycemic control. Some sulfonylureas have significant drug interactions with alcohol and some medications including warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole. A related isoform of ATP-sensitive potassium channels is present in the myocardium and the brain. All of these agents except glyburide have a low affinity for this isoform. Despite concerns that this agent might affect the myocardial response to ischemia and observational studies suggesting that sulfonylureas increase cardiovascular risk, the UKPDS did not show an increased cardiac mortality with glyburide.

Biguanides Metformin is representative of this class of agents. It reduces hepatic glucose production through an undefined mechanism and improves peripheral glucose utilization slightly (Table 338-11). Metformin reduces fasting plasma glucose and insulin levels, improves the lipid profile, and promotes modest weight loss. The initial starting dose of 500 mg once or twice a day can be increased to 1000 mg bid. An extended-release form is available and may have fewer gastrointestinal side effects (diarrhea, anorexia, nausea, metallic taste). Because of its relatively slow onset of action and gastrointestinal symptoms with higher doses, the dose should be escalated every 2–3 weeks based on SMBG measurements. The major toxicity of metformin, lactic acidosis, can be prevented by careful patient selection. Metformin should not be used in patients with renal insufficiency [serum creatinine > 133 μmol/L (1.5 mg/dL) in men or > 124 μmol/L (1.4 mg/dL) in women, with adjustments for age], any form of acidosis, CHF, liver disease, or severe hypoxia. Metformin should be discontinued in patients who are seriously ill, in patients who can take nothing orally, and in those receiving radiographic contrast material. Insulin should be used until metformin can be restarted.

α-Glucosidase Inhibitors α-Glucosidase inhibitors (acarbose and miglitol) reduce postprandial hyperglycemia by delaying glucose absorption; they do not affect glucose utilization or insulin secretion (Table 338-11). Postprandial hyperglycemia, secondary to impaired hepatic and peripheral glucose disposal, contributes significantly to the hyperglycemic state in type 2 DM. These drugs, taken just before each meal, reduce glucose absorption by inhibiting the enzyme that cleaves oligosaccharides into simple sugars in the intestinal lumen. Therapy should be initiated at a low dose (25 mg of acarbose or miglitol) with the evening meal and may be increased to a maximal dose over weeks to months (50–100 mg for acarbose or 50 mg for miglitol with each meal). The major side effects (diarrhea, flatulence, abdominal distention) are related to increased delivery of oligosaccharides to the large bowel and can be reduced somewhat by gradual upward dose titration. α-Glucosidase inhibitors may increase levels of sulfonylureas and decrease the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2.0 mg/dL). This class of agents is not as potent as other oral agents in lowering the hemoglobin A1C but is unique because it reduces the postprandial glucose rise even in individuals with type 1 DM. If hypoglycemia from other diabetes treatments occurs while taking these agents, the patient should consume glucose since the degradation and absorption of complex carbohydrates will be retarded.

Thiazolidinediones Thiazolidinediones reduce insulin resistance. These drugs bind to the PPAR-γ (peroxisome proliferator-activated receptor-γ) nuclear receptor. The PPAR-γ receptor is found at highest levels in adipocytes but is expressed at lower levels in many other tissues. Agonists of this receptor regulate a large number of genes, promote adipocyte differentiation, reduce hepatic fat accumulation, and appear to reduce insulin resistance indirectly by enhancing fatty acid storage and possibly by increasing adiponectin levels (Table 338-11). Thiazolidinediones promote a redistribution of fat from central to peripheral locations. Circulating insulin levels decrease with use of the thiazolidinediones, indicating a reduction in insulin resistance. Although direct comparisons are not available, the two currently available thiazolidinediones appear to have similar efficacy; the therapeutic range for pioglitazone is 15–45 mg/d in a single daily dose, and for rosiglitazone the total daily dose is 2–8 mg/d administered either once daily or twice daily in divided doses. The ability of thiazolidinediones to influence cardiovascular disease or other features of the metabolic syndrome is under investigation.

The prototype of this class of drugs, troglitazone, was withdrawn from the U.S. market after reports of hepatotoxicity and an association with an idiosyncratic liver reaction that sometimes led to hepatic failure. Although rosiglitazone and pioglitazone do not appear to induce the liver abnormalities seen with troglitazone, the FDA recommends measurement of liver function tests prior to initiating therapy with a thiazolidinedione and at regular intervals (every 2 months for the first year and then periodically). Rosiglitazone raises LDL, HDL, and triglycerides slightly. Pioglitazone raises HDL to a greater degree and LDL a lesser degree but lowers triglycerides. The clinical significance of the lipid changes with these agents is not known and may be difficult to ascertain since most patients with type 2 diabetes are also treated with a statin. Emphasis should be placed on reaching lipid, blood pressure, and glycemic targets rather than the type of therapy needed to reach those goals. Thiazolidinediones are associated with weight gain (2–3 kg), a small reduction in the hematocrit, and a mild increase in plasma volume. Peripheral edema and CHF may occur and is more common in individuals also treated with insulin. These agents are contraindicated in patients with liver disease or CHF (class III or IV). Recent metanalyses have suggested that rosiglitazone is associated with an increased risk of myocardial infarction. The FDA has issued an alert that rare patients taking these agents may experience a worsening of diabetic macular edema. An increased risk of fractures has been noted in women taking these agents. Thiazolidinediones have been shown to induce ovulation in premenopausal women with PCOS. Women should be warned about the risk of pregnancy, since the safety of thiazolidinediones in pregnancy is not established.

Insulin Therapy in Type 2 DM Insulin should be considered as the initial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic disease

not precludes oral glucose-lowering agents, or in individuals who are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops in patients with long-standing diabetes. Both physician and patient reluctance often delay the initiation of insulin therapy, but glucose control and patient well-being are improved by insulin therapy in patients who have not reached the glycemic target.

Because endogenous insulin secretion continues and is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of long-acting insulin (0.3–0.4 U/kg per day), given either before breakfast and in the evening (NPH) or just before bedtime (NPH, glargine, detemir). Since fasting hyperglycemia and increased hepatic glucose production are prominent features of type 2 DM, bedtime insulin is more effective in clinical trials than a single dose of morning insulin. Glargine given at bedtime has less nocturnal hypoglycemia than NPH insulin. Some physicians prefer a relatively low, fixed starting dose of intermediate-acting insulin (15–20 units in the morning and 5–10 units at bedtime) to avoid hypoglycemia. The insulin dose may then be adjusted in 10% increments as dictated by SMBG results. Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents (biguanides, α-glucosidase inhibitors, or thiazolidinediones). The combination of insulin and a thiazolidinedione promotes weight gain and edema and is a less desirable combination. Initially, basal insulin may be sufficient, but often prandial insulin coverage is needed as diabetes progresses. Other insulin formulations that have a combination of short-acting and long-acting insulin (Table 338-10) are sometimes used in patients with type 2 DM because of convenience but do not allow independent adjustment of short-acting and long-acting insulin dose. In selected patients with type 2 DM (usually insulin deficient as defined by C-peptide level), insulin infusion devices may be considered.

Agents That Enhance GLP-1 Receptor Signaling "Incretins" amplify glucose-stimulated insulin secretion. Agents that either act as a GLP-1 agonist or enhance endogenous GLP-1 activity have become available and are under development. Exenatide, a synthetic version of a peptide originally found in the saliva of the Gila monster (exendin-4), is an analogue of GLP-1. Unlike native GLP-1 which has a half-life of <5 min, differences in the exenatide amino acid sequence render it resistant to the enzyme that degrades GLP-1 (dipeptidyl peptidase IV, or DPP-IV). Thus, exenatide has prolonged GLP-1-like action by binding to GLP-1 receptors found in islets, the gastrointestinal tract, and the brain. Exenatide increases glucose-stimulated insulin secretion, suppresses glucagon, and slows gastric emptying. Exenatide does not promote weight gain; in fact, most patients experience modest weight loss. It appears that GLP-1 agonists also suppress appetite. Exenatide, approved for combination with other oral agents for type 2 DM, should be started as a 5-μg SC injection before the morning and evening meal and increased to 10 μg twice daily, depending on the response and side effects (nausea being the limiting factor). The A1C reductions with exenatide are modest compared to those with some oral agents. Exenatide is approved only for use as adjunct or combination therapy with metformin or sulfonylureas; studies of its efficacy in combination with other oral agents are underway. Exenatide should not be used in patients taking insulin. The major side effects are nausea, vomiting, and diarrhea; some patients taking insulin secretagogues may require a reduction in those agents to prevent hypoglycemia. Because it slows gastric emptying and may influence the absorption of other drugs, the timing of administration should be coordinated. Whether exenatide enhances beta cell survival, promotes beta cell proliferation, or alters the natural history of type 2 DM is not known. Other GLP-1 receptor agonists and formulations are under development. DPP-IV inhibitors represent a new class of oral agents that inhibit degradation of native GLP-1 and thus enhance incretin effect. These agents promote insulin secretion in the absence of hypoglycemia or weight gain, and appear to have a preferential effect on postprandial blood glucose. The FDA has approved the first DPP-IV inhibitor, sitagliptin, for use with diet and exercise to improve glycemic control in adult individuals with type 2 DM. It can also be used in combination with metformin or a thiazolidinedione. Sitagliptin is administered at a dose of 100 mg orally once daily. Reduced doses should be given to patients with moderate (creatinine clearance 30–50 mL/min, 50 mg once daily) or severe (creatinine clearance < 30 mL/min, 25 mg once daily) renal insufficiency. Renal function should be assessed prior to initiation of sitagliptin therapy and periodically thereafter. Clinical experience with this agent is limited.

Choice of Initial Glucose-Lowering Agent The level of hyperglycemia should influence the initial choice of therapy. Assuming maximal benefit of MNT and increased physical activity has been realized, patients with mild to moderate hyperglycemia [FPG < 11.1–13.9 mmol/L (200–250 mg/dL)] often respond well to a single, oral glucose-lowering agent. Patients with more severe hyperglycemia [FPG > 13.9 mmol/L (250 mg/dL)] may respond partially but are unlikely to achieve normoglycemia with oral monotherapy. A stepwise approach that starts with a single agent and adds a second agent to achieve the glycemic target can be used (see "Combination Therapy," below). Insulin can be used as initial therapy in individuals with severe hyperglycemia [FPG > 13.9–16.7 mmol/L (250–300 mg/dL)] or in those who are symptomatic from the hyperglycemia. This approach is based on the rationale that more rapid glycemic control will reduce "glucose toxicity" to the islet cells, improve endogenous insulin secretion, and possibly allow oral glucose-lowering agents to be more effective. If this occurs, the insulin may be discontinued.

Insulin secretagogues, biguanides, α-glucosidase inhibitors, thiazolidinediones, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has unique advantages and disadvantages, certain generalizations apply: (1) insulin secretagogues, biguanides, DPP-IV inhibitors, and thiazolidinediones improve glycemic control to a similar degree (1–2% reduction in A1C) and are more effective than α-glucosidase inhibitors; (2) assuming a similar degree of glycemic improvement, no clinical advantage to one class of drugs has been demonstrated, and any therapy that improves glycemic control is likely beneficial; (3) insulin secretagogues and α-glucosidase inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones are delayed by several weeks to months; (4) not all agents are effective in all individuals with type 2 DM (primary failure); (5) biguanides, α-glucosidase inhibitors, DPP-IV inhibitors, and thiazolidinediones do not directly cause hypoglycemia; and (6) most individuals will eventually require treatment with more than one class of oral glucose-lowering agents or insulin, reflecting the progressive nature of type 2 DM.

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

A reasonable treatment algorithm for initial therapy uses metformin as initial therapy because of its efficacy, known side-effect profile, and relatively low cost **(Fig. 338-15)**. Metformin has the advantage that it promotes mild weight loss, lowers insulin levels, and improves the lipid profile slightly. Based on SMBG results and the A1C, the dose of metformin should be increased until the glycemic target is achieved or maximum dose is reached.

Approximately one-third of individuals will reach their target glycemic goal using metformin as monotherapy.

Combination Therapy with Glucose-Lowering Agents A number of combinations of therapeutic agents are successful in type 2 DM, and the dosing of agents in combination is the same as when the agents are used alone. Because mechanisms of action of the first and second agents are different, the effect on glycemic control is usually additive. Several fixed dose combinations of oral agents are available, but evidence that they are superior to titration of single agent to a maximum dose and then addition of a second agent is lacking. If adequate control is not achieved with the combination of two agents (based on reassessment of the A1C every 3 months), a third oral agent or basal insulin should be added (Fig. 338-15).

Treatment with insulin becomes necessary as type 2 DM enters the phase of relative insulin deficiency (as seen in long-standing DM) and is signaled by inadequate glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used in patients who fail to reach the glycemic target. For example, a single dose of long-acting

insulin at bedtime is effective in combination with metfor endogenous insulin production falls further, multiple i of long-acting and short-acting insulin regimens are eg to control postprandial glucose excursions. These i mens are identical to the long-acting and short- e the bination regimens discussed above for type 1 D ese reg- hyperglycemia of type 2 DM tends to be more "st ays using imens can be increased in 10% increments ever e required the fasting blood glucose results. The daily ins ndogenous can become quite large (1–2 units/kg per da s. Individuals insulin production falls and insulin resistance ulin should be who require >1 unit/kg per day of long-act min or a thiazo- considered for combination therapy with hiazolidinedione lidinedione. The addition of metformin iduals with type 2 can reduce insulin requirements in som lycemic control. In- DM, while maintaining or even impro ght gain and is asso- sulin plus a thiazolidinedione promot a thiazolidinedione to ciated with peripheral edema. Addit e a reduction in the in- a patient's insulin regimen may ner sulin dose to avoid hypoglycemia

EMERGING THERAPIES pancreas transplantation (performed concomitantly wit hal transplant) may normal- portant therapeutic option in ize glucose tolerance and is stantial expertise and is associ- type 1 DM, though it requir unosuppression. Pancreatic islet ated with the side effects ued by limitations in pancreatic transplantation has beer al and remains an area of clinical islet isolation and graft uals with long-standing type 1 DM investigation. Many in lounts of insulin or have insulin-posi- still produce very sm reas. This suggests that beta cells are tive cells within the are quickly destroyed by the autoim- slowly regenerati fforts to suppress the autoimmune pro- mune process. Th beta cell regeneration are underway both at the time cess and to stim years after the diagnosis of type 1 DM. Closed-loop of diagnosis ar the appropriate amount of insulin in response to pumps that i levels are potentially feasible now that continuous glu- changing gl technology has been developed. cose-monit

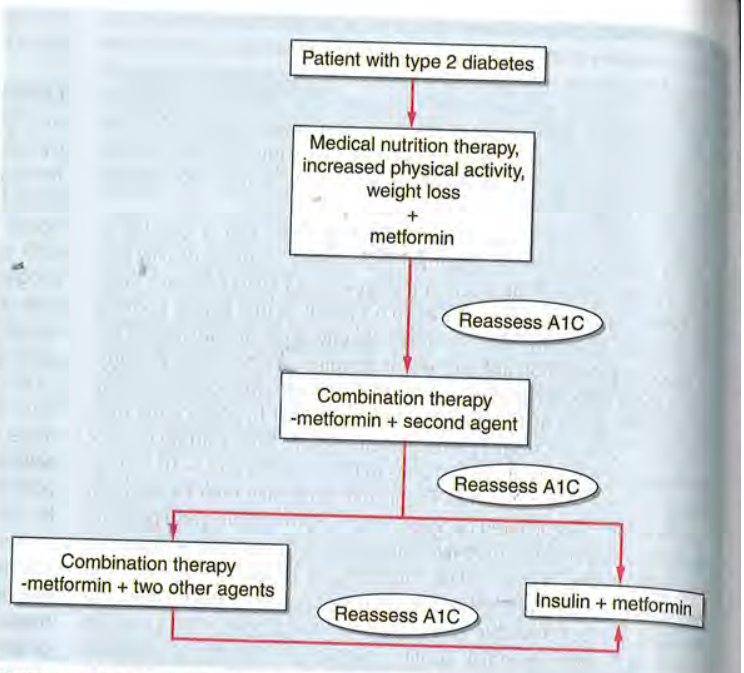


FIGURE 338-15 Glycemic management of type 2 diabetes. See text for discussion of treatment of severe hyperglycemia or symptomatic hyperglycemia. Agents that can be combined with metformin include insulin secretagogues, thiazolidinediones, α-glucosidase inhibitors, DPP-IV inhibitors, and exenatide. A1C, hemoglobin A1C.

COMP ATIONS OF THERAPY FOR DIABETES MELLITUS

As w any therapy, the benefits of efforts directed towards glycemic con must be weighed against the risks of treatment. Side effects of in ive treatment include an increased frequency of serious hypogly- c a, weight gain, increased economic costs, and greater demands on patient. In the DCCT, quality of life was very similar in the inten- ve and standard therapy groups. The most serious complication of therapy for DM is hypoglycemia, and its treatment with oral glucose or glucagon injection is discussed in Chap. 339. Severe, recurrent hypoglycemia warrants examination of treatment regimen and glycemic goal for the individual patient. Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin, α-glucosidase inhibitors, exenatide) therapies that improve glycemic control. It is partially due to the anabolic effects of insulin and the reduction in glucosuria. In the DCCT, individuals with the greatest weight gain exhibited increases in LDL cholesterol and triglycerides as well as increases in blood pressure (both systolic and diastolic) similar to those seen in individuals with type 2 DM and insulin resistance. These effects could increase the risk of cardiovascular disease. As discussed previously, transient worsening of diabetic retinopathy or neuropathy sometimes accompanies improved glycemic control.

ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE

The morbidity and mortality of DM-related complications can be greatly reduced by timely and consistent surveillance procedures (Table 338-13). These screening procedures are indicated for all individuals with DM, but numerous studies have documented that most individuals with diabetes do not receive comprehensive diabetes care. Screening for dyslipidemia and hypertension should be performed annually. In addition to routine health maintenance, individuals with diabetes should also receive the pneumococcal and tetanus vaccines (at recommended intervals) and the influenza vaccine (annually). As discussed above, aspirin therapy should be considered in many patients with diabetes.

An annual comprehensive eye examination should be performed by a qualified optometrist or ophthalmologist. If abnormalities are detected, further evaluation and treatment require an ophthalmologist skilled in diabetes-related eye disease. Because many individuals with type 2 DM have had asymptomatic diabetes for several years before diagnosis, the ADA recommends the following ophthalmologic examination schedule: (1) individuals with type 1 DM should have an initial eye examination within 3–5 years of diagnosis, (2) individuals with type 2 DM should have an initial eye examination at the time of diabetes diagnosis, (3) women with DM who are pregnant or contemplating pregnancy should have an eye examination prior to conception and during the first trimester, and (4) individuals whose eye examination is normal can have a repeat examination in 2–3 years rather than annually.

An annual foot examination should: (1) assess blood flow, sensation (monofilament testing, pin prick, or tuning fork), ankle reflexes, and nail care; (2) look for the presence of foot deformities such as hammer or claw toes and Charcot foot; and (3) identify sites of poten-

TABLE 338-13 GUIDELINES FOR ONGOING MEDICAL CARE FOR PATIENTS WITH DIABETES

- Self-monitoring of blood glucose (individualized frequency)
- A1C testing (2–4 times/year)
- Patient education in diabetes management (annual)
- Medical nutrition therapy and education (annual)
- Eye examination (annual)
- Foot examination (1–2 times/year by physician; daily by patient)
- Screening for diabetic nephropathy (annual; see Fig. 338-11)
- Blood pressure measurement (quarterly)
- Lipid profile and serum creatinine (estimate GFR) (annual)
- Influenza/pneumococcal immunizations
- Consider antiplatelet therapy (see text)

Note: A1C, hemoglobin A1C.

foot ulceration. Calluses and nail deformities should be treated by a podiatrist; the patient should be discouraged from self-care of even minor foot problems, but should be strongly encouraged to check his/her feet daily for any early lesions. The ADA advises a visual foot inspection in patients with symptoms or signs of diabetic neuropathy at 1- or 6-month intervals.

An annual microalbuminuria measurement (albumin-to-creatinine ratio in spot urine) is advised in individuals with type 1 or type 2 DM and no protein on a routine urinalysis (Fig. 338-10). If the urinalysis detects proteinuria, the amount of protein should be quantified by standard urine protein measurements. If the urinalysis was negative for protein in the past, microalbuminuria should be the annual screening examination. Routine urine protein measurements do not detect low levels of albumin excretion. Screening should commence 5 years after the onset of type 1 DM and at the time of diagnosis of type 2 DM. Regardless of protein excretion results, the GFR should be estimated using the serum creatinine in all patients on an annual basis.

SPECIAL CONSIDERATIONS IN DIABETES MELLITUS

PSYCHOSOCIAL ASPECTS

As with any chronic, debilitating disease, the individual with DM faces a series of challenges that affect all aspects of daily life. The individual with DM must accept that he or she may develop complications related to DM. Even with considerable effort, normoglycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. The patient should view him- or herself as an essential member of the diabetes care team and not as someone who is cared for by the diabetes team. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. This can lead to the appearance of either hyper- or hypoglycemia. Eating disorders, including binge eating disorders, bulimia, and anorexia nervosa, appear to occur more frequently individuals with type 1 or type 2 DM (Chap. 76).

MANAGEMENT IN THE HOSPITALIZED PATIENT

Virtually all medical and surgical subspecialties are involved in the care of hospitalized patients with diabetes. Hyperglycemia, whether in a patient with known diabetes or in someone without known diabetes, appears to be a predictor of poor outcome in hospitalized patients. General anesthesia, surgery, infection, or concurrent illness raises the levels of counterregulatory hormones (cortisol, growth hormone, catecholamines, and glucagon) and cytokines that may lead to transient insulin resistance and hyperglycemia. These factors increase insulin requirements by increasing glucose production and impairing glucose utilization and thus may worsen glycemic control. The concurrent illness or surgical procedure may lead to variable insulin absorption and also prevent the patient with DM from eating normally and may promote hypoglycemia. Glycemic control should be assessed (with A1C) and, if feasible, should be optimized prior to surgery. Electrolytes, renal function, and intravascular volume status should be assessed as well. The high prevalence of cardiovascular disease in individuals with DM (especially in type 2 DM) may require preoperative cardiovascular evaluation.

Glycemic control appears to improve the clinical outcomes in a variety of settings. In fact, many patients who do not have preexisting diabetes but who develop modest blood glucose elevations during their hospitalization appear to benefit from achieving near-normoglycemia using insulin treatment. For example, maintenance of a near-normal glucose with a continuous insulin infusion reduced the risk of postoperative infection after CABG and reduced the morbidity and mortality in patients in a surgical intensive care unit. In a number of cross-sectional studies of patients with diabetes, a greater degree of hyperglycemia was associated with worse cardiac, neurologic, and infectious outcomes. The goals of diabetes management during hospitalization are near-normoglycemia, avoidance of hypoglycemia, and transition back to the outpatient diabetes treatment regimen. The ADA suggests these glycemic goals for critically ill patients: ". . .as close to 6.1 mmol/L (110 mg/dL) and generally <10 mmol/L (180 mg/dL, postprandial)." In noncritically ill patients, the suggested glycemic goals are as close as possible to 5.0–7.2 mmol/L (90–130 mg/dL) preprandially and <10 mmol/L (180 mg/dL) postprandially. This process requires integrating information regarding the plasma glucose, diabetes treatment regimen, and clinical status of the patient.

The physician caring for an individual with diabetes in the perioperative period, during times of infection or serious physical illness, or simply when fasting for a diagnostic procedure must monitor the plasma glucose vigilantly, adjust the diabetes treatment regimen, and provide glucose infusion as needed. Depending on the severity of the patient's illness and the hospital setting, the physician can use either an insulin infusion or subcutaneous insulin. A "consistent carbohydrate diabetes meal plan" for hospitalized patients provides a predictable amount of carbohydrate for a particular meal each day (but not necessarily the same amount for breakfast, lunch, and supper). The hospital diet should be determined by a nutritionist; terms such as "ADA diet" or "low-sugar diet" are no longer used. Several different treatment regimens (IV or SC insulin regimens) can be employed successfully.

Insulin infusions can effectively control plasma glucose in the perioperative period and when the patient is unable to take anything by mouth. The absorption of subcutaneous insulin may be variable in such situations. Regular insulin is preferred over insulin analogues for IV insulin infusion since it is less expensive and equally effective. The physician must consider carefully the clinical setting in which an insulin infusion will be utilized, including whether adequate ancillary personnel are available to monitor the plasma glucose frequently and whether they can adjust the insulin infusion rate to maintain the plasma glucose within the optimal range.

Because of the short half-life of IV regular insulin, it is necessary to administer long-acting insulin prior to discontinuation of the insulin infusion to avoid a period of insulin deficiency. An alternative to an insulin infusion is basal or "scheduled" insulin provided by SC, long-acting insulin supplemented by prandial or "corrective" insulin using a short-acting insulin (insulin analogues preferred). The use of "sliding scale" insulin alone, where no insulin is given unless the blood glucose is elevated, is inadequate for in-patient glucose management and should not be used. The short-acting, pre-prandial insulin dose should include coverage for food consumption (based on anticipated carbohydrate intake) plus a corrective or supplemental insulin based on the patient's insulin sensitivity and the blood glucose. For example, if the patient is thin (and likely insulin sensitive), a corrective insulin supplement might be 1 unit for each 2.7 mmol/L (50 mg/dL) over the glucose target. If the patient is obese and insulin resistant, then the insulin supplement might be 2 units for each 2.7 mmol/L (50 mg/dL) over the glucose target. It is critical to individualize the regimen and adjust the basal or "scheduled" insulin dose frequently, based on the corrective insulin required.

Individuals with type 1 DM who are undergoing general anesthesia and surgery, or who are seriously ill, should receive continuous insulin, either through an IV insulin infusion or by SC administration of a reduced dose of long-acting insulin. Short-acting insulin alone is insufficient. Prolongation of a surgical procedure or delay in the recovery room is not uncommon and may result in periods of insulin deficiency leading to DKA. Insulin infusion is the preferred method for managing patients with type 1 DM in the perioperative period or when serious concurrent illness is present (0.5–1.0 units/h of regular insulin). Insulin-infusion algorithms jointly developed and implemented by nursing and physician staff are advised. If the diagnostic or surgical procedure is brief and performed under local or regional anesthesia, a reduced dose of SC, long-acting insulin may suffice (30–50% reduction, with short-acting insulin held or reduced). This approach facilitates the transition back to long-acting insulin after the procedure. Glucose may be infused to prevent hypoglycemia. The blood glucose should be monitored frequently during the illness or in the perioperative period.

Individuals with type 2 DM can be managed with either regular insulin infusion, or a reduced dose of SC long-acting insulin (25–50% reduction) plus preprandial, short-acting insulin. Oral glucose-lowering agents should be discontinued upon admission; they are not useful in regulating the plasma glucose in clinical situations where the insulin requirements and glucose intake are changing rapidly. Moreover, these oral agents may be dangerous if the patient is fasting (e.g., hypoglycemia with sulfonylureas). Metformin should be withheld when radiographic contrast media will be given or if there are CHF, acidosis, or declining renal function is present.

Total Parenteral Nutrition (See also Chap. 3.) Total parenteral nutrition (TPN) greatly increases insulin requirements. In addition, individuals not previously known to have DM may become hyperglycemic during TPN and require insulin treatment. Intravenous insulin infusion is the preferred treatment for hyperglycemia, and rapid titration to the required insulin dose is done most efficiently using a separate insulin infusion. After the total insulin dose has been determined, insulin may be added directly to the TPN solution or, preferably, given as a separate infusion. Often, individuals receiving either TPN or enteral nutrition receive their calorie loads continuously and not at "meal times"; consequently, SC insulin regimens must be adjusted.

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

Reproductive Issues Reproductive capacity in either men or women with DM appears to be normal. Menstrual cycles may be associated with alterations in glycemic control in women with DM. Pregnancy is associated with marked insulin resistance; the increased insulin requirements often precipitate DM and lead to the diagnosis of GDM. Glucose, which at high levels is a teratogen to the developing fetus, readily crosses the placenta, but insulin does not. Thus, hyperglycemia from the maternal circulation may stimulate insulin secretion in the fetus. The anabolic and growth effects of insulin may result in macrosomia. GDM complicates ~4% of pregnancies in the United States. The incidence of GDM is greatly increased in certain ethnic groups, including African Americans and Latinos, consistent with a similar increased risk of type 2 DM. Current recommendations advise screening for glucose intolerance between weeks 24 and 28 of pregnancy in women with high risk for GDM (≥25 years; obesity; family history of DM; member of an ethnic group such as Latino, Native American, Asian American, African American, or Pacific Islander). Therapy for GDM is similar to that for individuals with pregnancy-associated diabetes and involves MNT and insulin, if hyperglycemia persists. Oral glucose-lowering agents have not been approved for use during pregnancy. With current practices, the morbidity and mortality of the mother with GDM and the fetus are not different from those in the nondiabetic population. Individuals who develop GDM are at marked increased risk for developing type 2 DM in the future and should be screened periodically for DM. Most individuals with GDM revert to normal glucose tolerance after delivery, but some will continue to have overt diabetes or impairment of glucose tolerance. In addition, children of women with GDM appear to be at risk for obesity and glucose intolerance and have an increased risk of diabetes beginning in the later stages of adolescence.

Pregnancy in individuals with known DM requires meticulous planning and adherence to strict treatment regimens. Intensive diabetes management and normalization of the A1C are essential for individuals with existing DM who are planning pregnancy. The most crucial period of glycemic control is soon after fertilization. The risk of fetal malformations is increased 4–10 times in individuals with uncontrolled DM at the time of conception, and normal plasma glucose during the preconception period and throughout the periods of organ development in the fetus should be the goal.

LIPODYSTROPHIC DM

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

Protease Inhibitors and Lipodystrophy Protease inhibitors used in the treatment of HIV disease (Chap. 182) have been associated with a centripetal accumulation of fat (visceral and abdominal area), accumulation of fat in the dorsocervical region, loss of extremity fat, decreased insulin sensitivity (elevations of the fasting insulin level and reduced glucose tolerance on IV glucose tolerance testing), and dyslipidemia. Although many aspects of the physical appearance of these individuals resemble Cushing's syndrome, increased cortisol levels do not account for this appearance. The possibility remains that this is related to HIV infection by some undefined mechanism, since some features of the syndrome were observed before the introduction of protease inhibitors. Therapy for HIV-related lipodystrophy is not well established.

FURTHER READINGS

AMERICAN DIABETES ASSOCIATION: Clinical practice recommendations 2007. Diabetes Care 30:S4, 2007

———: Nutrition recommendations and interventions for diabetes—2006. Diabetes Care 29:2140, 2006

BAX JJ et al: Screening for coronary artery disease in patients with diabetes. Diabetes Care 30:2729, 2007

BOLEN S et al: Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 147:386, 2007

EISENBARTH GS: Update in type 1 diabetes. J Clin Endocrinol Metab 92:2403, 2007

GROSS JL et al: Diabetic nephropathy: Diagnosis, prevention, and treatment. Diabetes Care 28:164, 2005

INZUCCHI SE: Management of hyperglycemia in the hospital setting. N Engl J Med 355:1903, 2006

NATHAN DM et al: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 353:2643, 2005

SAUDEK CD et al: Assessing glycemia in diabetes using self-monitoring blood glucose and hemoglobin A1c. JAMA 295:1688, 2006

STUMVOLL M et al: Type 2 diabetes: Principles of pathogenesis and therapy. Lancet 365:1333, 2005

VINIK A et al: Diabetic neuropathies: Clinical manifestations and current treatment options. Nat Clin Pract Endocrinol Metab 2:269, 2006

ZIMMET P et al: Global and societal implications of the diabetes epidemic. Nature 414:782, 2001