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416 Diabetes Mellitus: Management and Therapies

Diabetes Mellitus:

Management and

Therapies Alvin C. Powers, Kevin D. Niswender,

Michael R. Rickels OVERALL GOALS The goals of therapy for all forms of diabetes mellitus (DM) are to (1) eliminate symptoms related to hyperglycemia, (2) reduce or eliminate the long-term microvascular and macrovascular complications of DM (Chap. 417), and (3) allow the patient to achieve as normal a lifestyle as possible. To reach these goals, the physician and health care team should identify a target level of glycemic control for each patient, pro vide the patient with the educational and pharmacologic resources nec essary to reach this target, avoid hypoglycemia, and monitor/prevent/ treat DM-related complications. Symptoms of diabetes usually resolve when the plasma glucose is <11.1 mmol/L (200 mg/dL), and thus most DM treatment focuses on achieving the second and third goals. The care of an individual with either type 1 or type 2 DM requires a multidisciplinary team. Central to the success of this team are the patient's participation, input, and enthusiasm, all of which are essential for optimal diabetes management. Members of the health care team usually include the primary care provider and/or the endocrinologist or diabetologist, an advanced practice provider (APP), a pharmacist, a certified diabetes educator, a nutritionist, a behavioral health pro fessional, and possibly a social worker. In addition, when the com plications of DM arise, subspecialists (including ophthalmologists, neurologists, podiatrists, nephrologists, cardiologists, and cardiovascu lar and transplant surgeons) with experience in DM-related complica tions are essential. The American Diabetes Association (ADA) suggests applying the Chronic Care Model to diabetes with an emphasis on these elements: a proactive, team-based delivery and health system design that involves self-management, decision support with evidencebased guidelines for person-specific and population-based approaches, and community resources and policies that support healthy lifestyles. Space limitations do not allow a discussion of all these elements, so this chapter first reviews the ongoing treatment of diabetes in the outpa tient setting and then discusses the treatment of severe hyperglycemia, as well as the treatment of diabetes in hospitalized patients. ONGOING ASPECTS OF COMPREHENSIVE DIABETES CARE A

number of names are sometimes applied to different approaches to diabetes care, such as intensive insulin therapy or intensive glycemic control. The current chapter, and other sources, uses the term Compre hensive diabetes care to emphasize the fact that optimal diabetes therapy involves much more than glucose management and medications and that individualized, patient-centered care is essential. Although glyce mic control is central to optimal diabetes therapy, comprehensive dia betes care of both type 1 and type 2 DM should also detect and modify risk factors for DM-associated disorders and manage DM-specific complications (Chap. 417). The key elements of comprehensive diabe tes care are summarized in Table 416-1. The morbidity and mortality of DM can be greatly reduced by timely and consistent surveillance, including the detection, prevention, and management of DM-related complications (Table 416-1 and Chap. 417). Such approaches are indi cated for all individuals with DM, but many individuals with diabetes do not receive these or comprehensive diabetes care. The social deter minants of health and family, financial, cultural, and employmentrelated issues may negatively impact diabetes care. This chapter, while recognizing that resources available for diabetes care vary widely throughout the world, provides guidance for comprehensive diabe tes care in health care settings with considerable societal resources.

TABLE 416-1 Guidelines for Ongoing, Comprehensive Medical Care for Individuals with Diabetes • Individualized glycemic goal and therapeutic plan with an emphasis on shared decision-making • Blood glucose measurement using continuous glucose monitoring (CGM) or capillary fingerstick device • HbA1c testing (2–4 times/year) • Lifestyle management in the care of diabetes, including: • Diabetes self-management education and support • Nutrition therapy • Physical activity • Psychosocial care, including evaluation for depression, anxiety, diabetes Diabetes Mellitus: Management and Therapies
CHAPTER 416 distress • Detection, prevention, or management of diabetes-related complications, including: • Diabetes-related eye examination (annual or biannual; Chap. 417) • Diabetes-related foot examination (1–2 times/year by provider; daily by patient; Chap. 415) • Diabetes-related neuropathy examination (annual; Chap. 415) • Diabetes-related kidney disease testing (annual; Chap. 417) • Screen for other diabetes-related complications (annual; see Table 417-1) • Assessment of fracture risk in older adults with diabetes (consider measurement of bone mineral density) • Manage or treat diabetes-relevant conditions, including: • Blood pressure (assess 2–4 times/year; Chap. 417) • Lipids (1–2 times/year; Chap. 417) • Consider screening individuals with type 2 diabetes or prediabetes for metabolic dysfunction–associated steatotic liver disease if other risk factors are present • Consider antiplatelet therapy with low-dose aspirin (Chap. 417) • Immunizations, including influenza, pneumococcal, hepatitis B, coronavirus, and respiratory syncytial virus (>60 years of age) (Chap. 6) Abbreviation: HbA1c, glycated hemoglobin A1c.
Patient-oriented websites also offer important resources for patients and their caregivers. Examples of these resources include: https://www. tidepool.org/about; https://diatribe.org/understanding-diabetes/diabetestechnology; and https://pro.diabeteswise.org/en/. Lifestyle Management in Diabetes Care The patient with type 1 or type 2 DM should receive education about nutrition, physical activity, psychosocial support, care of diabetes during illness, medications used to control the glucose, methods for glucose monitoring, and strategies to prevent diabetes-related complications. Patient education allows and encourages individuals with DM to assume greater responsibility for their care, leading to improved compliance. Diabetes Self-Management Education and Support (DSMES) DSMES refers to ways to improve the patient’s knowl edge, skills, and abilities necessary for diabetes self-care and should

also emphasize psychosocial issues and emotional well-being. Patient education is a continuing process with regular visits for reinforcement; it is not a process completed after one or two visits. It should receive special emphasis at the diagnosis of diabetes, annually, or at times when diabetes treatment goals are not attained, and during transitions in life or medical care. DSMES is delivered by a diabetes educator who is a health care professional (nurse, dietician, or pharmacist) with specialized patient-education skills and who is certified in diabetes education (e.g., Association of Diabetes Care and Education Specialists or Certification Board for Diabetes Care and Education). Education topics important for optimal diabetes self-care include continuous glucose monitoring (CGM) or blood glucose monitoring (BGM); urine or blood ketone monitoring (type 1 DM); insulin administra tion; guidelines for diabetes management during illnesses; prevention and management of hypoglycemia (Chap. 418); foot and skin care; diabetes management before, during, and after exercise; and risk factor–modifying activities. The focus is providing patient-centered, individualized education. More frequent contact between the patient

and the diabetes management team (e.g., electronic, telephone, video) improves glycemic control.

Nutrition Therapy 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 (e.g., insulin, exercise, and weight loss). Some aspects of MNT are directed at preventing or delaying the onset of type 2 DM in high-risk individuals (obese or with prediabetes) by promoting weight reduction. Other measures of MNT are directed at improving glycemic control through monitoring car bohydrate intake, avoiding simple sugars and fructose, and managing diabetes-related complications (atherosclerotic cardiovascular disease [ASCVD], nephropathy). Medical treatment of obesity, including phar macologic approaches that facilitate weight loss and metabolic surgery, should be considered in some patients (Chaps. 413 and 414). PART 12 Endocrinology and Metabolism In general, the components of optimal MNT are similar for individ uals with type 1 or type 2 DM—high-quality, nutrient-dense foods with limits on carbohydrate intake and weight management (Table 416-2). The data are currently inconclusive about various eating patterns (e.g., intermittent fasting). Sleep deprivation and shift work are risk factors for weight gain and insulin resistance. Dietary advice should be individualized, acknowledging personal preferences, cultural, and religious traditions. Use of the glycemic index, an estimate of the post prandial rise in the blood glucose when a certain amount of that food is consumed, may reduce postprandial glucose excursions and improve glycemic control. The goal of MNT in type 1 DM is to coordinate and match the car bohydrate intake, both temporally and quantitatively, with the appro priate amount of insulin. MNT in type 1 DM is informed by CGM and/or BGM that should be integrated to define the optimal insulin regimen. Based on the patient’s estimate of the carbohydrate content of TABLE 416-2 Nutritional Recommendations for Adults with Diabetes or Prediabetesa General dietary guidelines • Vegetables, fruits, whole grains, legumes, low-fat dairy products and food higher in fiber and lower in glycemic content; optimal diet composition and eating pattens are not known. Fat in diet (optimal percentage of diet is not known; should be individualized) • Encourage Mediterranean-style diet rich in monounsaturated and polyunsaturated fatty acids. • Minimal or no trans fat consumption. Carbohydrate in diet (optimal percentage of diet is not known; should be individualized) • Monitor carbohydrate intake in regard to calories and set limits for meals to reduce postprandial glycemia. • Consider limiting overall carbohydrate intake in adults with diabetes as this may improve glycemia. • Avoid fructose- and sucrose-containing beverages and minimize consumption of foods with added sugar that may displace healthier, more nutrient-dense

food choices and elevate postprandial glycemia. • Estimate grams of carbohydrate in diet for flexible insulin dosing (type 1 diabetes and insulin-dependent type 2 diabetes). • Consider using glycemic index to predict how consumption of a particular food may affect blood glucose. Protein in diet (optimal percentage of diet is not known; should be individualized) Other components • Reduced-calorie and nonnutritive sweeteners may be useful. • Routine supplements of vitamins, antioxidants, or trace elements not supported by evidence. • Vitamin D and calcium supplemental as recommended to promote bone health. • Sodium intake as advised for general population (<2300 mg/d). • Minimize disruption to sleep and eating patterns (chrononutrition), and note risk of hypoglycemia associated with religious fasting. aSee text for differences for patients with type 1 or type 2 diabetes. Source: Data from American Diabetes Association: Facilitating positive health behaviors and well-being to improve health outcomes: Standards of care in diabetes—2024. Diabetes Care 47:S77, 2024.

a 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 variations in caloric intake. An important component of MNT in type 1 DM is to minimize the weight gain often associated with intensive insulin therapy and is best achieved by placing limits on carbohydrate intake. The goals of MNT in type 2 DM should focus on weight loss 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. Very-low-carbohydrate diets that induce weight loss may result in rapid and dramatic glucose lowering in individuals with new-onset type 2 DM. MNT for type 2 DM should emphasize mod est caloric reduction, increased physical activity, and weight loss (goal of at least 5–10% loss). Weight loss and exercise each independently improve insulin sensitivity. Fasting for religious reasons, such as during Ramadan, presents a chal lenge for individuals with diabetes, especially those taking medications to lower the plasma glucose. Under most guidelines for fasting during Ramadan, individuals are risk-stratified based on a pre-Ramadan risk assessment for people with diabetes as those who can safely fast with medi cal evaluation and supervision and those in whom fasting is not advised. Thus, patient education and regular glucose monitoring are critical. Physical Activity 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 moderate aerobic physical activity with no gaps longer than 2 days. Resistance exercise, flexibility and balance training, and reduced sedentary behavior throughout the day are also advised. Despite its benefits, exercise may present challenges for some individuals with DM because they lack the normal glucoregulatory mechanisms (normally, insulin falls and glucagon rises during exer cise). 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 pre-exercise plasma glucose, the circulating insulin level, lactate, and the level of exercise-induced catecholamines. If the insulin level is too low, the delivery of lactate to the liver and 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 (see below related to CGM and possible blood glucose dis cordance); (2) delay exercise if blood glucose is >14 mmol/L (250 mg/ dL) and ketones are present; (3) if the blood glucose is <5.0 mmol/L (90 mg/dL), ingest carbohydrate before exercising; (4) monitor glu cose during exercise and ingest carbohydrate as needed to prevent hypoglycemia; (5) decrease insulin doses (based on previous experi ence) before and after exercise and inject insulin into a nonexercising area; and (6) learn individual glucose responses to different types 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. Untreated proliferative retinopathy is a relative contraindication to vigorous exercise because this may lead to vitreous hemorrhage or retinal detachment (Chap. 417). Psychosocial Care Because the individual with DM faces chal lenges that affect many aspects of daily life, psychosocial assessment and support are a critical part of comprehensive diabetes care. The patient should view himself/herself/themself as an essential member of the diabetes care team and not as someone who is cared for by the

diabetes management team. Even with considerable effort, normo glycemia can be an elusive goal, and solutions to worsening glycemic control may not be easily identifiable. Depression, anxiety, or “diabetes distress,” defined by the ADA as “negative psychological reactions related to emotional burdens … in having to manage a chronic dis ease like diabetes,” should be recognized and may require the care of a mental health specialist. Emotional stress may provoke a change in behavior so that individuals no longer adhere to a dietary, exercise, or therapeutic regimen. Eating disorders, including binge eating disor ders, bulimia, and anorexia nervosa, appear to occur more frequently in individuals with type 1 or type 2 DM. ■ ■MONITORING THE LEVEL OF GLYCEMIC CONTROL Optimal monitoring of glycemic control involves CGM or BGM (blood collected by fingerstick) by the patient and an assessment of long-term control by providers using measurement of hemoglobin A1c (HbA1c). These measurements are complementary: the patient’s measurements provide a picture of short-term glycemic control, whereas the HbA1c reflects average glycemic control over the previous 2–3 months. By integrating glycemic measurements with diet and exercise history into comprehensive diabetes care, the diabetes management team and patient can improve glycemic control and reduce diabetes-related complications. Assessment of Short-Term Glycemic Control All individu als with diabetes should be offered a device to assess their short-term patterns of glycemia. CGM technology utilizes a sensor or electrode to detect interstitial glucose, which is in equilibrium with the blood glucose but may lag when the blood glucose changes rapidly or during exercise. Glucose sensors are placed subcutaneously by the patient and replaced every 10–14 days; a different device can be placed subcutane ously by a minor surgical procedure and replaced every 6–12 months. Some CGMs require calibration by fingerstick blood glucose measure ment. CGM provides glucose data every 5 minutes, and the device’s output can be provided in an ambulatory glucose profile (AGP) that is a standardized, single page summary that includes the percentage of time in the desired glycemic range (TIR, or time in range), the per centage of time above the target range, the percentage of time below the target range, the glucose management indicator (GMI), which correlates with HbA1c (Table 416-3), and glucose variability. CGM in real time also allows the patient to monitor the trend of glucose change (upward or downward), with this trend being used to avoid predicted hyper- or hypoglycemia. CGM device technology is rapidly evolving with the number of available CGM devices increasing and features expanding. This chapter uses the term CGM to encompass both

real-time CGM and intermit tently scanned CGM, with real-time CGM being more effective. Most CGMs require a provider’s prescription, but CGM devices are approved for purchase without a provider’s prescription. The selection of CGM type should consider the implications for the individual with diabetes (e.g., cost, convenience, insurance coverage), the provider (e.g., access to patient’s CGM data), and the health system (e.g., integration of patient CGM data into the electronic medical record). Selection is best optimized by the involvement of a certified diabetes educator TABLE 416-3 Relationship of HbA1c and Estimated Average Glucose (eAG) ESTIMATED AVERAGE GLUCOSE (AVERAGE, RANGE) HEMOGLOBIN A1C (%) mmol/L mg/dL

5.4 (4.2–6.7) 97 (76–120)

7.0 (5.5–8.5) 126 (100–152)

8.6 (6.8–10.3) 154 (123–185)

10.2 (8.1–12.1) 183 (147–217)

11.8 (9.4–13.9) 212 (170–249)

13.4 (10.7–15.7) 240 (193–282)

14.9 (12.0–17.5) 269 (217–314)

16.5 (13.3–19.3) 298 (240–347) Source: Data adapted from Diabetes Care 31:1473, 2008.

knowledgeable about these technologies. Unfortunately, certified dia betes educators are not available in all care settings, so the individual with diabetes and the provider may need to investigate CGM options using online resources and see suggestions in the reference list. Many are vendor specific; some resources provide information on multiple vendors, technologies, and devices. The selection of a CGM device should be individualized based on patient preference and skill level, capability to collect and use the data, and ability to upload data to adjust therapy. CGM may be used in individuals whose diabetes is partially or completely managed by someone else, such as a caregiver (e.g., in a child or an individual with cognitive impairment). After the selection of a CGM device, the individual with diabetes (and/or the caregiver) should receive education and training on a regular basis.

 BGM devices use a small drop of blood (<2 µL) and an enzymatic reaction to rapidly measure the capillary blood glucose. It is critical that individuals using CGM also have a capillary (fingerstick) device for times when the CGM technology is malfunctioning, CGM results are questionable, or for CGM calibration (if required or desired). Substances can interfere with the accuracy of measurements by CGM devices (e.g., hydroxyurea, acetaminophen, ascorbic acid, mannitol, and sorbitol) and BGM devices (e.g., uric acid, galactose, xylose, acet aminophen, L-DOPA, or ascorbic acid). Individuals with type 1 DM or individuals with type 2 DM taking insulin injections each day should monitor their blood glucose by CGM. CGM in type 1 DM, especially in those with hypoglycemia unawareness, can decrease the frequency of serious hypoglycemia (especially nocturnal hypoglycemia). The combination of an insulininfusion device (discussed

below) and a CGM can automate insulin delivery with either predictive suspension of insulin delivery to avoid hypoglycemia or closed-loop control that automatically adjusts insulin delivery by a predictive algorithm (Fig. 416-1). Some CGM/insulin pump manufacturers offer the patient a way to upload glucose data into the manufacturer's server, which can then be securely accessed by the provider's staff. It is critical for the patient's glycemic data to be securely accessible to the provider and uploaded into the electronic health record of the provider and health system, but approaches and systems to accomplish this need further improvement. Individuals with type 2 DM treated on oral therapy and/or only with diet/lifestyle require less intense glycemic monitoring and can use CGM or BGM to measure the glucose at a lower frequency (e.g., 3–5 times/week). Many individuals with type 1 or type 2 DM report that real-time access to glycemic information via CGM assists in lifestyle choices, diet, and activity in addition to insulin or medication manage ment, thereby improving control. Assessment of Long-Term Glycemic Control Measurement of glycated hemoglobin (HbA1c) is the standard method for assess ing long-term glycemic control. When plasma glucose is consistently elevated, there is an increase in nonenzymatic glycation of hemo globin; this alteration reflects the glycemic history over the previous 2–3 months, because erythrocytes have an average life span of ~120 days (glycemic level in the preceding month contributes about 50% to the HbA1c value). Laboratory standards for the HbA1c test should be corre lated to the reference assay of the Diabetes Control and Complications Trial (DCCT). Measurement of HbA1c at the "point of care" allows for more rapid feedback and may therefore assist in adjustment of therapy. As the primary predictor of long-term complications of DM, the HbA1c should mirror the short-term measurement by CGM or BGM. HbA1c should be measured in all individuals with DM during their initial evaluation and as part of their comprehensive diabetes care. In patients achieving their glycemic goal, the ADA recommends measure ment of the HbA1c at least twice per year. More frequent testing (every 3 months) is warranted when glycemic control is inadequate or when therapy has changed. The HbA1c correlates with the average plasma glucose value or estimated average glucose (eAG) (Table 416-3) but does not detect glycemic variability or recent intercurrent illnesses as CGM or BGM can. There is interindividual variability in the HbA1c to mean glucose relationship, likely genetically determined; there is con troversy and some uncertainty about the influence of race or ancestry

PART 12 Endocrinology and Metabolism A B FIGURE 416-1 Glycemic monitoring and insulin administration options for treatment of diabetes. A. Continuous glucose monitoring (CGM) profile and delivery of rapidacting insulin analogue by continuous subcutaneous insulin infusion pump involves a basal rate (light purple line) and prandial and correction boluses (purple circles) based on estimated carbohydrate intake (orange squares) and an insulin sensitivity factor. B. CGM profile with sensor-communicating insulin pump that automates insulin delivery by suspending delivery for predicted hypoglycemia and increasing basal delivery for predicted hyperglycemia (light purple curves) while still requiring user input for estimated carbohydrate intake (orange squares) to provide prandial insulin boluses (purple circles). C. CGM profile is used to generate an estimate of time-in-range with glycemic goal shown on the left side of the bar and target percent time in that glycemic range shown on the right side of the bar. D. Pharmacokinetic profile of selected insulin formulations. The duration of action of an insulin may vary among individuals. (Part C: Reproduced with permission from T Battelino et al: Clinical targets for continuous glucose monitoring data interpretation: Recommendations from the International Consensus on Time in Range. Diabetes Care 42:1593, 2019; Part D: Reproduced with permission from JJ Neumiller: Insulin Update: New and Emerging Insulins, American Diabetes Association, 2018.) on HbA1c. For example, the HbA1c

in African Americans is slightly higher (~0.3%) than in non-Hispanic white or Hispanic individuals for the same mean glucose. Clinical conditions leading to abnormal red blood cell (RBC) parameters such as hemoglobinopathies, anemias, reticulocytosis, transfusions, uremia, variants in glucose-6-phosphate dehydrogenase, hemodialysis, erythropoietin therapy, and HIV treat ment may alter the HbA1c result. Glycemic control can also be assessed by the degree of glycation of other proteins, such as fructosamine or glycated albumin, that reflect glycemia over the prior 2–4 weeks. PHARMACOLOGIC TREATMENT OF DIABETES Comprehensive care of type 1 and type 2 DM requires an emphasis on nutrition, exercise, and monitoring of glycemic control in addition to glucose-lowering medication(s). Medications to prevent and man age diabetes-related complications are discussed in Chap. 417. This chapter discusses classes of such medications but does not describe all glucose-lowering agents available worldwide. The initial step is to select an individualized glycemic goal for the patient. ■ ■ESTABLISHMENT OF TARGET LEVEL OF GLYCEMIC CONTROL Because the complications of DM are related to glycemic control, nor moglycemia or near-normoglycemia is the desired, but often elusive, goal for most patients. Normalization or near-normalization of the plasma glucose for long periods of time had been extremely difficult, as demonstrated by the DCCT and United Kingdom Prospective Diabetes Study (UKPDS), but new technologies and medications are making this goal more feasible. Regardless of the level of hyperglycemia, improve ment in glycemic control will lower the risk of diabetes-related com plications, most notably the microvascular complications (Chap. 417). The target for glycemic control (as reflected by the HbA1c) should be individualized, and the goals of therapy should be developed in consul tation with the individuals with diabetes after considering a number of medical, social, and lifestyle issues (ADA terms this patient-centered care) such as age, ability to understand and implement a treatment

Type 1 & Type 2 Diabetes Target <5% <250 mg/dL (13.9 mmol/L)

> 180 mg/dL (10.0 mmol/L) <25% Target Range: 70–180 mg/dL (3.9–10.0 mmol/L) 70% <70 mg/dL (3.9 mmol/L) <54 mg/dL (3.0 mmol/L) C <4% <1% Rapid (aspart, lispro, glulisine, inhaled human insulin) Short (regular U-100) Mixed short/intermediate (regular U-500) Intermediate (NPH) Plasma Insulin Levels Long (U-100 glargine) Ultra-long (degludec)

10 12 14 16 18 Time (hr) 20 22 24 26 28 30 32 34 36 D regimen, presence and severity of complications of diabetes such as ASCVD, ability to recognize hypoglycemic symptoms, presence of other medical conditions or treatments that might affect survival or the response to therapy, lifestyle and occupation (e.g., possible conse quences of experiencing hypoglycemia on the job), and level of support available from family and friends. In general, the ADA suggests that the goal is to achieve an HbA1c as close to normal as possible without significant hypoglycemia. In most individuals, the target HbA1c should be <7% (Table 416-4) with a more stringent (≤6.5%) target for some patients. With current treatment and devices, the level of HbA1c is no longer inversely related to the frequency and severity of hypoglycemia as seen in the DCCT. A higher HbA1c target of <7.5 or 8% is appropriate for individuals with cognitive impairment, those with reduced ability to sense hypoglycemia, or those with limited life span, realizing that these factors represent a spectrum across individuals (Table 416-4). Approximately one in four individuals over the age of 65

years has diabetes. Thus, the glycemic goal in elderly individuals (>65 years) should be individualized and consider the over all clinical state of the individual. For example, in an elderly individual with robust cognition and few major health issues, the glycemic goal may be the same as in younger individuals (HbA1c target <7.0%), while in an individual with impaired cognition or a resident of a long-term facility, the major goal is avoidance of hypoglycemia and severe hyper glycemia (Table 416-4). Large clinical trials (UKPDS, Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], Veterans Affairs Diabetes Trial [VADT]; DCCT/EDIC study in type 1 DM; see Chap. 417) examined glycemic control in type 2 DM in indi viduals with low risk of ASCVD, a high risk of ASCVD, or established ASCVD. Overall, these studies indicate that (1) improved glycemic control reduces microvascular complications of diabetes; (2) improved glycemic control in individuals early in the course of type 1 DM led to reduction in nonfatal myocardial infarction, stroke, and cardiovascular death almost two decades after the period of improved glycemic con trol had ended; (3) intense glycemic control is beneficial for ASCVD in

TABLE 416-4 Glycemic Goals for Adults with Diabetesa INDEX OF GLYCEMIC CONTROL ADULTS (NONPREGNANT) HbA1c <7.0% (53 mmol/mol) <7.0–7.5% (53–57 mmol/mol) <8.0% (64 mmol/mol) <8.5% (64 mmol/mol) with avoidance of hypoglycemia

> 70% within 3.9–10.0 mmol/L (70–180 mg/dL)c CGM metrics % Time within indicated rangec Time below 3.9 mmol/L (70 mg/dL) but 54 mg/dL (>3 mmol/L) indicating level 1 or mild hypoglycemia)c Time below <54 mg/dL (<3 mmol/L) indicating level 2 or moderate/severe hypoglycemiac Glucose variability, % coefficient of variationd <4% <1% ≤36% Preprandial capillary blood glucose 4.4–7.2 mmol/L (80–130 mg/dL) Postprandial capillary blood glucosee <10.0 mmol/L (<180 mg/dL) <11.1 mmol/L (200 mg/dL) <13.9 mmol/L (250 mg/dL) <13.9 mmol/L (250 mg/dL) aGlycemic goal should be individualized for each patient; elderly >65 years. Some suggest different glycemic targets such as the American Association of Clinical Endocrinology (AACE), which suggests an HbA1c goal <6.5%, and American College of Physicians (ACP), which suggests a goal of 7–8%. bMultiple chronic illnesses, impaired activities of daily living, or cognitive impairment. cOverall poor health with complex comorbidities, cognitive impairment, or limited life span or resident in skilled nursing facility or a long-term care facility. dAs determined by CGM. See Chap. 418 for hypoglycemia definitions. e1–2 h after beginning of a meal. Abbreviations: CGM, continuous glucose monitoring; HbA1c, hemoglobin A1c; N/A, not applicable to glycemia management. Source: Adapted from several sources, including Diabetes Care 47:S111, 2024, and Diabetes Care 47:S244, 2024. some populations with type 2 DM; and (4) hypoglycemia in high-risk populations with ASCVD should be avoided as it is associated with cardiovascular events and mortality. Thus, near-normal glycemia is not the goal in this population (Table 416-4). As will be discussed later, these studies were conducted before the advent of glucagon-like peptide 1 (GLP-1) receptor agonists (GLP-1RAs) and sodium-glucose cotransporter 2 (SGLT-2) inhibitors,

> which have greater cardiovascular benefit than agents utilized in these earlier clinical trials. ■ ■TYPE 1 DIABETES MELLITUS General Aspects The goal is to design and implement an insulin regimen that mimics physiologic insulin secretion. Because individu als with type 1 DM partially or completely lack endogenous insulin production, administration of basal insulin is essential for regulat ing glycogen breakdown, gluconeogenesis, lipolysis, and ketogenesis (e.g., fine-tuning hepatic and adipose metabolism). Likewise, insulin replacement for meals should be appropriate for the carbohydrate intake and insulin sensitivity, promoting normal glucose utilization and storage. The continued increase in insulin costs over the past decade has been a major challenge for individuals with diabetes. Recent federal and state legislative action has begun to address this; however, the cost of insulin continues to be a major issue in diabetes care. Intensive Management of Glycemia Intensive insulin therapy in type 1 DM seeks to achieve normal or near-normal glycemia. This goal requires the integration of multiple resources and efforts, includ ing thorough and continuing patient education, comprehensive record ing of glucose measurements and nutrition intake by the patient, and a variable insulin regimen that matches carbohydrate intake and exercise and insulin dose. Insulin is delivered subcutaneously via multiple daily injections (MDIs), continuous subcutaneous insulin infusion (CSII), a sensor-augmented system, or an automated insulin delivery system (AID). Insulin delivery by CSII requires a manual entry into the pump to alter the basal infusion rate or direct an insulin bolus. A sensor-augmented system has a pump and a CGM device, assisted by an algorithm that suspends the insulin infusion when the glucose is low or predicted to be low in 30 min based on the glucose trajec tory. An AID system, using a pump, CGM, and algorithm, increases or decreases the basal insulin infusion rate in real time based on CGM data. Some AID systems deliver a correction insulin bolus, but these

ELDERLY ADULTS WITH COMPLEX COMORBIDITIES, POOR HEALTH, OR IMPARIED COGNITIONc ELDERLY ADULTS WITH INTACT COGNITION AND FUNCTIONAL STATUS ELDERLY ADULTS WITH OTHER SERIOUS COMORBIDITIESb

> “ 70% within 4.4–10.0 mmol/L (80–180 mg/dL)c 50% within 5.5–10.0 mmol/L (100–200 mg/dL)c 40% within 6.7–12.2 mmol/L (120–220 mg/dL)c Diabetes Mellitus: Management and Therapies
> CHAPTER 416 <1% <1% <33% 0% 0% N/A 0% 0% N/A 4.4–7.2 mmol/L (80–130 mg/dL) 5.0–8.3 mmol/L (90–150 mg/dL) 5.6–10.0 mmol/L (100–180 mg/dL) TABLE 416-5 Properties of Insulin Preparationsa TIME OF ACTION EFFECTIVE DURATION, h PREPARATION ONSET, h PEAK, h Rapid-acting, injected Aspartb <0.25 0.5–1.5 3–5 Glulisine <0.25 0.5–1.5 3–5 Lisproc <0.25 0.5–1.5 3–5 Short-acting, injected Regulard 0.5–1.0 2–3

4–8	Rapid-acting, inhaled	Inhaled human insulin	<0.25	1–2

Intermediate-acting, injected NPH 2–4 4–10 10–16 Long-acting or Ultralong-acting, injected Degludec 1–9 —e 42f Glargineg 2–4 —e 20–24 Examples of insulin combinationsh 75/25–75% protamine lispro, 25% lispro <0.25 Duali 10–16 70/30–70% protamine aspart, 30% aspart <0.25 Duali 15–18 50/50–50% protamine lispro, 50% lispro <0.25 Duali 10–16 70/30–70% NPH, 30% regular 0.5–1 Duali 10–16 Combination of long-acting insulin and GLP-1RA See text aInjectable insulin preparations (with exception of inhaled formulation) available in the United States; others are available in the United Kingdom and Europe. Standard formulations are U-100 (100 units of insulin per mL solution). Insulin detemir, a long-acting insulin, will soon not be available and is not included in this table. bFormulation with niacinamide (vitamin B3) has a slightly more rapid onset and offset. cLispro-aabc formulation has a slightly more rapid onset and offset. Several forms of insulin (e.g., degludec, insulin lispro, Lispro-aabc) are also available in U-200 concentration. dFormulation also available in U-500 concentration with delayed onset and offset. eDegludec and glargine have minimal peak activity. dDuration is dose-dependent. gFormulation also available in U-300 concentration, which has longer duration. hOther insulin combinations are available. iDual: two peaks—one at 2–3 h and the second one several hours later. Abbreviations: GLP-1RA, glucagon-like peptide 1 receptor agonist; NPH, neutral protamine Hagedorn.

are not a completely closed-loop system as the patient must input carbohydrate intake data and projected activity or exercise. This is a rapidly evolving area of type 1 DM–related technology, algorithms, and artificial intelligence, with some individuals having considerable success using do-it-yourself (DIY) approaches that are based in the type 1 DM user community and not U.S. Food and Drug Administra tion (FDA) approved.

The benefits of intensive insulin therapy and improved glycemic control include a reduction in the acute metabolic and chronic micro vascular complications of DM. From a psychological standpoint, the patient experiences greater control over their diabetes and often notes an improved sense of well-being, greater flexibility in the timing and content of meals, and the capability to alter insulin dosing with exer cise. Intensive insulin therapy prior to and during pregnancy reduces the risk of fetal malformations and morbidity. Intensive insulin therapy is encouraged in newly diagnosed patients with type 1 DM, including the use of CGM. Although intensive management confers impressive benefits, it may not be appropriate at all times for all individuals with T1D (Table 416-4). Some individuals with diabetes prefer subcutane ous, intermittent insulin injections combined with a CGM to being connected continuously to an insulin infusion device, highlighting the need for individualized diabetes care. PART 12 Endocrinology and Metabolism Insulin Preparations Insulin preparations are generated by recombinant DNA technology and consist of the amino acid sequence of human insulin or variations thereof. In the United States, most insulin is formulated as U-100 (100 units/mL); short-acting insulin formulated as U-200 (200 units/mL; lispro) and long-acting as U-300 (300 units/mL; glargine) are available in order to limit injection vol umes for patients with high insulin requirements. Regular insulin formulated as U-500 (500 units/mL) is sometimes used in patients with severe insulin resistance. Human insulin has been formulated with dis tinctive pharmacokinetics (regular and neutral protamine Hagedorn [NPH] insulin have the native insulin amino acid sequence) or geneti cally modified to alter insulin absorption and hence the onset and duration of insulin action. Insulins can be classified as rapid-acting, short-acting,

intermediate-acting, long-acting, or ultralong-acting (Table 416-5; Fig. 416-1D). For example, one rapid-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. Insulin aspart and insulin glulisine are modified insulin analogues with properties similar to lispro. A biosimilar version of lis pro is available. 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 character istics are particularly advantageous for allowing entrainment of insulin injection and action to the 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, leading to the for mation of microprecipitates at physiologic pH in subcutaneous tissue. Compared to NPH insulin, the onset of insulin glargine action is later, the duration of action is longer (~24 h), and there is a less pronounced peak. A lower incidence of hypoglycemia, especially at night, has been reported with insulin glargine when compared to NPH insulin. A biosimilar version is available. Twice-daily injections of glargine are sometimes required to provide optimal 24-h basal insulin coverage. Because of modification and extension of the carboxy-terminus of the B chain, insulin degludec forms multihexamers in subcutaneous tissue and binds albumin, prolonging its duration of action (>42 h); it provides similar glycemic control as glargine but with less frequent nocturnal and severe hypoglycemia. Other modified insulins, such as one with a duration of action of 1 week, are in clinical trials and will likely soon be available.

Basal insulin requirements, largely fine-tuning hepatic glucose metabolism, are provided by long-acting insulin formulations (NPH insulin, insulin glargine, or insulin degludec) (Fig. 416-1D; Table 416-5). These are usually prescribed with rapid-acting insulin in an attempt to mimic physiologic insulin release with meals (prandial insulin require ment). In the past, NPH and short-acting insulin formulations were mixed in the same syringe, but this is not common now. The miscibil ity of some insulins 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). By including the insulin analogue mixed with protamine, several additional combinations have a rapid-acting and long-acting profile (Table 416-5; Fig. 416-1D). Although more convenient for the patient (only two injections a day), combination insulin formulations do not allow independent adjustment of shortacting and long-acting activity and are not appropriate in type 1 DM management. Most insulin formulations are available as insulin “pens,” which are more convenient and accurate than syringes; “smart pens” can assist with insulin dose tracking. Insulin delivery by inhalation to provide mealtime insulin has a more rapid onset of action than insulin injected subcutaneously. Prior to its use, the forced expiratory volume in 1 s (FEV1) should be measured, and then monitored periodically during treatment. Inhaled insulin can cause bronchospasm and cough and should not be used by individuals with lung disease or those who smoke. Long-acting insulin/GLP-1RA combinations in fixed doses (degludec plus liraglutide or glargine plus lixisenatide) are effective and are associated with less weight gain. Insulin Regimens There is considerable patient-to-patient varia tion in the peak and duration. In all regimens, long-acting insulins (NPH, glargine, or degludec) supply basal insulin, whereas regular, insulin aspart, glulisine, or lispro provide prandial insulin (Fig. 416-1D; Table 416-5). Rapid-acting insulin analogues should be injected just before (<10 min) and regular insulin 30–45 min prior to a

meal. Sometimes rapid-acting insulin analogues are injected just after a meal (gastroparesis, unpredictable food intake). A consensus statement from ADA and the European Association for the Study of Diabetes provides guidance about different insulin regimens used in type 1 DM. A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous insu lin is secreted into the portal venous system. Thus, exogenous insulin administration exposes the liver to subphysiologic insulin levels, and requires achieving higher peripheral levels of insulin to restrain hepatic glucose production. No current 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 rapid-acting insulin, and CGM or more frequent BGM. In general, individuals with type 1 DM require 0.4–1.0 units/kg per day of insulin divided into multiple doses, with 30–50% of daily insulin given as basal insulin with the remainder as prandial insulin. All individuals with type 1 DM should have a filled glucagon prescription (Chap. 416). MDI regimens refer to the combination of basal insulin and bolus insulin (preprandial rapid-acting insulin). The timing and dose of rapid-acting, preprandial insulin are altered to accommodate the CGM or BGM results, anticipated food intake, and physical activity. Such regimens offer the patient with type 1 DM more flexibility in terms of lifestyle and the best chance for achieving near normoglycemia. Most often, basal insulin with glargine or degludec is used in conjunction with preprandial lispro, glulisine, or insulin aspart. The dose of longacting insulin is adjusted based on the fasting glucose. 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-to-carbohydrate ratio (a common ratio for type 1 DM is 1 unit/10–15 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 1.6–3.3 mmol/L [30–60 mg/dL] over the preprandial glucose target; this correction factor can be estimated from 1500/[total daily insulin dose]). Such

TABLE 416-6 Agents Used for Treatment of Type 1 or Type 2 Diabetes MECHANISM OF ACTION EXAMPLESa HBA1C REDUCTION (%)b AGENT-SPECIFIC ADVANTAGES Oral Metformin 1–2 Weight neutral, do not cause hypoglycemia, inexpensive, extensive experience, modest

↓ CV events Biguanidesc* ↓ Hepatic glucose production, ↑ insulin sensitivity, influence gut function Sodium-glucose cotransporter 2 (SGLT-2) inhibitorsc*** Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, bexagliflozin, sotagliflozin (SGLT-1/2 inhibitor) 0.5–1.0 Renal protective,

↓ CV events, ↓ heart failure, do not cause hypoglycemia, modest ↓ weight and blood pressure ↑ Renal glucose excretion Dipeptidyl peptidase-4 inhibitorsc*** Prolong endogenous GLP-1 action;

↑ insulin, ↓ glucagon Alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin 0.5–0.8 Well tolerated, do not cause hypoglycemia Insulin secretagogues: Sulfonylureasc* ↑ Insulin secretion Glimepiride, glipizide, gliquidone, glyburide 1–2 Short onset of action, lower postprandial glucose, inexpensive Insulin secretagogues: Nonsulfonylureasc*** ↑ Insulin secretion Nateglinide, repaglinide 0.5–1.0 Short onset of action, lower postprandial glucose Thiazolidinedionesc**** ↓ Insulin resistance,

Pioglitazone, rosiglitazone 0.5–1.4 Lower insulin requirements ↑ glucose utilization Acarbose, miglitol 0.5–0.8 Reduce postprandial glycemia α-Glucosidase inhibitorsc** ↓ GI glucose absorption Parenteral/Oral (GLP-1RA-related agents) Dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide (oral formulation available) 0.5–1.0 Weight loss, do not cause hypoglycemia (unless combined with another insulin secretagogue or insulin); ↓ CV events, modest renoprotection GLP-1RAsc*** ↑ Insulin, ↓ glucagon, slow gastric emptying, satiety GLP-1/GIP receptor agonistc*** ↑ Insulin, ↓ glucagon, slow gastric emptying, satiety Tirzepatide 1.8-2.4 Weight loss, do not cause hypoglycemia (unless combined with insulin secretagogue or insulin); ↓ CV events Parenteral Amylin agonistsc,d*** Slow gastric emptying, ↓ glucagon Pramlintide 0.25–0.5 Reduce postprandial glycemia, weight loss See text and Table 416-4 Not limited Known safety profile Injection, weight gain, hypoglycemia Insulinc,d**** ↑ Glucose utilization, ↓ hepatic glucose production, and other anabolic actions Medical nutrition therapy and physical activityc* Low-calorie, carbohydratecontrolled diet, exercise 1–3 Other health benefits Compliance difficult, long-term success of sustained weight loss low ↓ Insulin resistance, ↑ insulin secretion aExamples are approved for use in the United States; others are available in other countries. Examples may not include all agents in the class. bHbA1c reduction (absolute) depends partly on starting HbA1c. cUsed for treatment of type 2 diabetes. dUsed in conjunction with insulin for treatment of type 1 diabetes. Cost of agent in the United States: *low, **moderate, ***high, ****variable. eDegree of risk uncertain, avoid in individuals with risk factors for pancreatitis. fRisk of euglycemic DKA in patients with insulin deficiency. Note: Some agents used to treat type 2 diabetes are not included in table (see text). Abbreviations: CHF, congestive heart failure; CV, cardiovascular; DKA, diabetic ketoacidosis; GFR, glomerular filtration rate; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; GLP-1RA, glucagon-like peptide 1 receptor agonist; HbA1c, glycated hemoglobin A1c.

AGENT-SPECIFIC DISADVANTAGES CONSIDERATIONS Diarrhea, nausea, lactic acidosis, vitamin B12 deficiency Renal insufficiency (see text for GFR <30 mL/min), CHF, radiographic contrast studies, hospitalized patients, acidosis Diabetes Mellitus: Management and Therapies
CHAPTER 416 Increased risk genital mycotic infections and necrotizing fasciitis of perineum; polyuria, dehydration; increased risk of euglycemic DKAf (see text); exacerbate tendency to hyperkalemia Moderate renal insufficiency; discontinue 3–4 days before surgery, during serious illness Angioedema/urticarial and immune-mediated dermatologic effects; rarely associated with pancreatitis Reduced dose with renal insufficiency Hypoglycemia, weight gain Renal/liver insufficiency Hypoglycemia Renal/liver insufficiency (except repaglinide) Peripheral edema, CHF, weight gain, fractures, macular edema CHF, renal/liver insufficiency GI flatulence, elevated liver function tests Renal/liver insufficiency Nausea, GI intolerance; possibly associated with pancreatitise, possibly worsen retinopathy Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, previous ileus Nausea, GI intolerance, possibly associated pancreatitise, possibly worsen retinopathy Renal disease, agents that also slow GI motility; medullary carcinoma of thyroid, pancreatic disease, history of gastroparesis Agents that also slow GI motility Injection, nausea, ↑ risk of hypoglycemia with insulin Can be combined with most other agents Other health benefits

calculations must be adjusted based on each individual’s sensitiv ity to insulin. CGM or BGM is essential for these types of insulin regimens.

AID is the preferred insulin delivery mechanism for most indi viduals with type 1 DM (Fig. 416-1), but cost and insurance coverage are critical considerations. To the basal insulin infusion, a prepran dial insulin (“bolus”) is delivered by the insulin infusion device based on instructions from the patient or an algorithm that incorporates the preprandial plasma glucose and anticipated carbohydrate intake. These sophisticated devices can accurately deliver small doses of insulin (microliters per hour) and have several advantages: (1) multi ple basal infusion rates can be programmed to accommodate noctur nal 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 algo rithms consider ongoing action of prior insulin administration and blood glucose values in calculating the insulin dose. As mentioned, the technology, algorithms, and integration of the different compo nents are changing rapidly, indicating the need to match these with patients’ desires, for instruction by a health professional with con siderable experience with insulin infusion devices, and for frequent patient interactions with the diabetes management team. Insulin infusion devices may present unique challenges, such as infection at the infusion site, unexplained hyperglycemia because the infusion set becomes obstructed, or diabetic ketoacidosis (DKA) if the insulin infusion device becomes disconnected. Because most physicians use lispro, glulisine, or insulin aspart in CSII or AID, the short half-life of these insulins quickly leads to insulin deficiency if the delivery system is interrupted. Essential to the safe use of infusion devices is thorough patient education, CGM or frequent BGM, and a backup plan for injecting long- and/or rapid-acting insulins in the event of insulin infusion device failure. CGM sensor-augmented insulin infusion devices integrate the information from the CGM to inform insulin delivery (Fig. 416-1). Currently, sensor communicating functions can interrupt basal insulin delivery during hypoglycemia (threshold suspension) or when hypoglycemia is anticipated (predic tive suspension), which may be particularly useful for preventing nocturnal hypoglycemia. Hybrid closed-loop systems can combine patient-directed preprandial boluses with automated adjustment of between-meal and basal insulin delivery based on CGM. Clini cal experience with closed-loop systems is rapidly increasing and expanding. Bihormonal infusion devices that deliver both insulin and glucagon are being tested. PART 12 Endocrinology and Metabolism Other Agents That Improve Glucose Control The role of amylin, a 37-amino-acid peptide co-secreted with insulin from pan creatic 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 individuals with type 1 or type 2 DM 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 or type 2 DM. The addition of pramlintide produces a modest reduction in the HbA1c and seems to dampen meal-related glucose excursions. In type 1 DM, pramlintide is started as a 15-μg SC injec tion 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 medica tions and should not be used in combination with other drugs that slow gastrointestinal (GI) motility. The rapid-acting insulin given before the meal should initially be reduced to avoid hypoglycemia and then titrated as the effects of the pramlintide become evident. Because pramlintide suppresses glucagon, it may worsen hypoglyce mia recovery and should not be used in patients with hypoglycemia

Management of Type 2 Diabetes Screen for/manage complications of diabetes • Retinopathy • Nephropathy • Neuropathy • Cardiovascular disease • Other complications Treat associated conditions • Dyslipidemia • Hypertension • Obesity Individualized glycemic control • Diet/lifestyle • Exercise • Medication FIGURE 416-2 Essential elements in comprehensive care of type 2 diabetes. unawareness. GLP-1RAs and SGLT-2 inhibitors modestly improve the HbA1c in type 1 DM, but the SGLT-2 inhibitors increase the risk of DKA and in general should not be used. ■ ■TYPE 2 DIABETES MELLITUS General Aspects The goals of glucose-directed therapy for type 2 DM are similar to those in type 1 DM and, likewise, should be individ ualized for each patient. Whereas glycemic control tends to dominate the management of type 1 DM, the care of individuals with type 2 DM must also include even greater attention to the treatment of conditions associated with type 2 DM (e.g., obesity, hypertension, dyslipidemia, ASCVD) and prevention/detection/management of DM-related com plications (Fig. 416-2; Chap. 417). Reduction in cardiovascular risk is of paramount importance because this is the leading cause of mortal ity in these individuals. One approach to pharmacology of glucosedirected therapies in type 2 DM is shown in Fig. 416-3. Type 2 DM 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. Any therapy that improves glycemic control reduces “glucose toxicity” to beta cells and may improve endogenous insulin secretion. However, type 2 DM is a progressive disorder and ultimately requires multiple therapeutic agents and sometimes insulin. Glucose-Lowering Agents Advances in the therapy of type 2 DM have led to glucose-lowering agents that target different pathophysi ologic 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, act as a GLP-1 receptor agonist, or promote urinary excretion of glucose (Table 416-6). Insulin is sometimes the initial glucose-lowering agent in type 2 DM if there is severe hyperglycemia or the patient is catabolic. BIGUANIDES Metformin, representative of this class of agents, reduces hepatic glucose production and improves peripheral glucose utiliza tion slightly (Table 416-6) and is relatively low cost. Metformin acts in multiple tissues, but its mechanism of action remains incompletely defined. Metformin reduces fasting plasma glucose (FPG) and insulin levels, improves the lipid profile, and promotes modest weight loss. An extended-release form is available and may have fewer GI side effects (diarrhea, anorexia, nausea, metallic taste). Because of metformin’s relatively slow onset of action and GI symptoms with higher doses, the initial dose should be low and then escalated every 1–2 weeks to a maximally tolerated dose of 2000 mg daily. Metformin is effective as monotherapy and can be used in combination with other glucose lowering agents. The major toxicity of metformin, lactic acidosis, is very rare and can be prevented by careful patient selection. Vitamin B12 levels are lower during metformin treatment and should be moni tored. Metformin should not be used in patients with moderate renal insufficiency (glomerular filtration rate [GFR] <30 mL/min), any form of acidosis, unstable congestive heart failure (CHF), liver disease, or

severe hypoxemia. Metformin should be discontinued in hospitalized patients, in patients who can take nothing orally, and in those receiving radiographic contrast material. Insulin should be used as needed until metformin can be restarted. INSULIN SECRETAGOGUES—AGENTS THAT AFFECT THE ATP-SENSITIVE K+ CHANNEL Insulin secretagogues stimulate insulin secretion by interacting with the ATP-sensitive potassium channel on the beta cell (Chap. 415). These drugs are most effective in individuals with type 2 DM of relatively recent onset (<5 years) who have residual endogenous

insulin production. Sulfonylureas reduce both fast ing and postprandial glucose and should be initiated at low doses and increased at 1- to 2-week intervals based on CGM or BGM. Glimepiride and glipizide can be given in a single daily dose and are preferred over glyburide, especially in the elderly. Repaglinide and nateglinide are not sulfonylureas but also interact with the ATPsensitive potassium channel. Because of their short half-life, these glinide agents are given immediately before each meal to reduce meal-related glucose excursions. Insulin secretagogues, especially the longer-acting ones, have the potential to cause 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 hypogly cemia and should be monitored closely in the hospital (Chap. 418). Most sulfonylureas are metabolized in the liver to compounds (some of which are active, such as those of glyburide and the glinide nateg linide) that are cleared by the kidney. Thus, their use in individuals with significant hepatic or renal dysfunction is not advisable. For patients with chronic kidney disease the glinide repaglinide may be used with caution. 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 interac tions with alcohol and some medications including warfarin, aspirin, ketoconazole, α-glucosidase inhibitors, and fluconazole. Sulfonylureas interact with some antibiotics such as fluoroquinolones, clarithromy cin, sulfamethoxazole-trimethoprim, metronidazole, and fluconazole, so the sulfonylureas should be discontinued when these antimicrobials are added to the patient’s medications. GLP-1RAS ALONE OR IN COMBINATION WITH GIP RECEPTOR AGONIST

“Incretins” amplify glucose-stimulated insulin secretion and suppress inappropriate glucagon secretion (Chap. 415). Agents that either act as a GLP-1RA or enhance endogenous GLP-1 activity are approved for the treatment of type 2 DM and obesity (Table 416-6). Agents in this class do not cause hypoglycemia because of the glucose-dependent nature of incretin-stimulated insulin secretion (unless there is concomitant use of an agent that can lead to hypoglycemia—sulfonylureas, etc.). GLP1RAs increase glucose-stimulated insulin secretion, suppress glucagon, and slow gastric emptying, but the GLP-1 receptor is expressed in several tissues, including the brain. These agents promote weight loss (see Chaps. 413 and 414) and reduce cardiovascular events in those with type 2 DM and ASCVD (see Chap. 417 for additional discussion about the effect on diabetes-related complications). Thus, these agents are particularly advantageous in type 2 DM. Long-acting GLP-1RAs include sustained-release exenatide, dulaglutide, lixisenatide, and sema glutide, all administered weekly, and are the ones most commonly used. Daily oral semaglutide is available that allows gastric absorption to avoid proteolytic degradation in the small intestine. All are modified to avoid enzymatic inactivation by dipeptidyl peptidase IV (DPP-4) in the circulation. Higher doses of liraglutide and semaglutide than used for glucose-lowering effects are effective for weight-loss therapy for obesity. Liraglutide treatment has also been associated with a decrease in cardio vascular disease (CVD) events in patients with type 2 DM and established CVD and with lower rates of diabetic kidney disease. In similar patient populations, semaglutide treatment has been associated with fewer CVD events and reduced diabetic kidney disease, but with an increased rate of retinopathy-related complications. Dulaglutide treatment has been associated with both a reduction in CVD events and a reduc tion in composite microvascular retinopathy and nephropathy-related

complications primarily driven by prevention of renal events. Treatment with GLP-1RAs should start at a low dose to minimize initial side effects (nausea being the limiting one). GLP-1RAs can be used as combination therapy with metformin, sulfonylureas, and thiazolidinediones. Some patients taking insulin or an insulin secretagogue may require a reduc tion in those agents to prevent hypoglycemia. The major side effects are nausea and vomiting. Some formulations carry a black box warning from the FDA because of an increased risk of thyroid C-cell tumors in rodents and are contraindicated in individuals with medullary carcinoma of the thyroid or multiple endocrine neoplasia. Because GLP-1RAs slow gastric emptying, they may influence the absorption of other drugs. Whether GLP-1RAs enhance beta cell survival or promote beta cell proliferation is not known. It is not clear if these agents alter the natural history of type 2 DM.

Diabetes Mellitus: Management and Therapies

CHAPTER 416 Tirzepatide, a once-weekly subcutaneous injectable peptide engi neered to have dual agoniism at both the glucose-dependent insulino tropic polypeptide receptor (GIPR) and the GLP-1R, promotes greater weight loss than a GLP-1RA alone. Additional dual-acting and tripleacting molecules are in development and clinical trials. DPP-4 inhibitors inhibit degradation of native GLP-1 and GIP and thus enhance the incretin effect. DPP-4, which is widely expressed on the cell surface of endothelial cells and some lymphocytes, degrades a wide range of peptides (not incretin specific). DPP-4 inhibitors pro mote insulin secretion in the absence of hypoglycemia or weight gain and appear to have a preferential effect on postprandial blood glucose. The levels of GLP-1 action in the patient are greater with the GLP-1RAs than with DPP-4 inhibitors. DPP-4 inhibitors are used either alone or in combination with other oral agents in type 2 DM. Reduced doses should be given to patients with renal insufficiency. Allergy, including rash, hypersensitivity reactions (including anaphylaxis, angioedema, and Stevens-Johnson syndrome), and severe joint pain have been reported in association with DPP-4 inhibitors. There is evidence con cerning a potentially increased risk for acute pancreatitis with GLP1RAs and less so with DPP-4 inhibitors. It is prudent to avoid these agents in patients with pancreatic disease or with other significant risk factors for acute pancreatitis (e.g., heavy alcohol use, severely elevated serum triglycerides, hypercalcemia). SGLT-2 INHIBITORS These agents (Table 416-6) lower the blood glu cose by selectively inhibiting this co-transporter, which is expressed almost exclusively in the proximal convoluted tubule in the kidney. This inhibits glucose reabsorption, lowers the renal threshold for glucose excretion, and leads to increased urinary glucose loss. Thus, the glucose-lowering effect is insulin independent and not related to changes in insulin sensitivity or secretion. The loss of urinary glucose may promote modest weight reduction. Since these agents also impair proximal reabsorption of sodium, their use is associated with a diuretic effect and a 3- to 6-mmHg reduction in systolic blood pressure. Due to the increased urinary glucose, urinary and genital mycotic infections are more common in both men and women, and the diuretic effect can lead to reduced intravascular volume and acutely impaired kidney function. Inhibition of SGLT-2 may lead to increased glucagon and, consequently, liver production of glucose and ketones. Euglycemic DKA may occur during illness or when ongoing glucosuria masks stress-induced requirements for insulin. Patients should be educated about this possibility, and providers should be vigilant about detec tion. These agents should not be prescribed for patients with type 1 DM or pancreatogenic forms of DM associated with insulin deficiency. Empagliflozin or canagliflozin reduces ASCVD events and all-cause cardiovascular mortality in patients with type 2 DM and established ASCVD. SGLT-2 inhibitors may reduce hospitalization for CHF. Empagliflozin, canagliflozin, and dapagliflozin have all been shown to reduce progression of diabetic kidney disease but should not be initi ated in patients with stage 3b

chronic kidney disease (CKD; estimated GFR [eGFR] <45 mL/min per 1.73 m2) and should not be used in stage 4 CKD (eGFR <30 mL/min per 1.73 m2). A possible increased risk of bladder cancer has been seen with dapagliflozin. The impact of SGLT-2 inhibitors on diabetes-related complications is discussed in Chap. 417 and below.

THIAZOLIDINEDIONES Thiazolidinediones (Table 416-6) reduce insulin resistance by binding to the peroxisome proliferator-activated receptor γ (PPAR-γ) nuclear receptor (which forms a heterodimer with the retinoid X 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 pro mote fatty acid storage. 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.

Rosiglitazone raises low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides slightly. Pioglitazone raises HDL to a greater degree and LDL to a lesser degree but lowers triglycerides. The clinical significance of the lipid changes with these agents is not known. PART 12 Endocrinology and Metabolism 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 are more common in individuals treated with these agents. These agents are contraindicated in patients with hepatic insufficiency or CHF (class III or IV). 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 postmenopausal women taking these agents. Thiazolidinedio nes have been shown to induce ovulation in premenopausal women with polycystic ovary syndrome. Women should be warned about the risk of pregnancy because the safety of thiazolidinediones in pregnancy is not established. According to an FDA review, pioglitazone may be associated with an increased risk of bladder cancer. In one study, pio glitazone lowered the risk for recurrent stroke or myocardial infarction in insulin-resistant individuals without diabetes who had a prior stroke or transient ischemic attack. `-GLUCOSIDASE INHIBITORS α-Glucosidase inhibitors reduce post prandial hyperglycemia by delaying glucose absorption (Table 416-6). Postprandial hyperglycemia, secondary to impaired hepatic and periph eral 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 with the evening meal and increased to a maximal dose over weeks to months. 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 titra tion. α-Glucosidase inhibitors may increase levels of sulfonylureas and increase the incidence of hypoglycemia. Simultaneous treatment with bile acid resins and antacids should be avoided. These agents should not be used in individuals with inflammatory bowel disease, gastroparesis, or a serum creatinine >177 μmol/L (2 mg/dL). This class of agents is not as potent as other oral agents in lowering the HbA1c but is unique because it reduces the postprandial glucose rise. If hypoglycemia from other diabetes treatments occurs while taking these agents, the patient should consume glucose because the degradation and absorption of complex carbohydrates will be slowed. OTHER THERAPIES FOR TYPE 2 DM • Bile Acid–Binding Resins

Evidence indicates that bile acids, by signaling through nuclear recep tors, may have a role in metabolism. Bile acid metabolism is abnormal in type 2 DM. The bile acid–binding resin colesevelam has been approved for the treatment of type 2 DM (already approved for treat ment of hypercholesterolemia). The role of this class of drugs in the treatment of type 2 DM is not yet defined. Bromocriptine A formulation of the dopamine receptor agonist bro mocriptine (Cycloset) has been approved by the FDA for the treat ment of type 2 DM. However, its role in the treatment of type 2 DM is uncertain. INSULIN THERAPY IN TYPE 2 DM Insulin should be considered for ini tial therapy in type 2 DM, particularly in lean individuals or those with severe weight loss, in individuals with underlying renal or hepatic dis ease that precludes oral glucose-lowering agents, or in individuals who

are hospitalized or acutely ill. Insulin therapy is ultimately required by a substantial number of individuals with type 2 DM because of the progressive nature of the disorder and the relative insulin deficiency that develops with long-standing diabetes. Both physician and patient reluctance often delay the initiation of insulin therapy, but glucose control and individual well-being are improved by insulin therapy in patients who have not reached their glycemic target. Because endogenous insulin secretion is capable of providing some coverage of mealtime caloric intake, insulin is usually initiated in a single dose of long-acting insulin (0.1–0.4 U/kg per day), given in the evening or just before bedtime (NPH, glargine, or degludec). Because 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 long-acting insulin (10–15 units) or a weight-based dose (0.1 units/kg). The insulin dose may then be adjusted in 10–20% increments as dictated by CGM or BGM results. Both morning and bedtime long-acting insulin may be used in combination with oral glucose-lowering agents. Initially, basal insulin may be sufficient, but often prandial insulin coverage with multiple insulin injections is needed as diabetes progresses (see insulin regimens used for type 1 DM). Other insulin formulations that have a combination of rapid-acting and long-acting insulin (Table 416-5) are sometimes used in patients with type 2 DM because of convenience but do not allow independent adjustment of rapid-acting and long-acting insulin dose and often do not achieve the same degree of glycemic control as basal/bolus regimens. AID in selected individuals with type 2 DM should be considered, especially in those who are insulindeficient. CGM should be used in all individuals taking insulin. CHOICE OF INITIAL GLUCOSE-LOWERING AGENT The level of hyper glycemia and the patient’s individualized goal (see “Establishment of Target Level of Glycemic Control”) should influence the initial choice of therapy. Patients with mild hyperglycemia (FPG <7.0– 11.0 mmol/L [126–199 mg/dL]) often respond well to a single, oral glucose-lowering agent, while those with moderate hyperglycemia (FPG 11.1–13.9 mmol/L [200–250 mg/dL]) will usually require more than one oral agent or insulin. Patients with more severe hyperglyce mia (FPG >13.9 mmol/L [250 mg/dL]) may respond partially but are unlikely to achieve normoglycemia with oral therapy. 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 symptom atic 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. Treatment algorithms by several profes sional societies (ADA/ European Association for the Study of Diabetes [EASD], International Diabetes Federation, American Association of Clinical Endocrinology) suggest metformin as initial

therapy because of its efficacy, known side effect profile, and low cost (Fig. 416-3). Initiation of pharmacologic therapy should be accompanied by an emphasis on lifestyle modification (e.g., MNT, increased physical activ ity, and weight loss). Metformin's advantages are that it promotes mild weight loss, lowers insulin levels, and improves the lipid profile slightly. Based on CGM or BGM results and the HbA1c, the dose of metformin should be increased until the glycemic target is achieved or the maxi mum dose is reached. GLP-1RAs and SGLT-2 inhibitors are increasing in use as evidence accumulates for CVD and CKD benefits, in addition to weight loss and glucose-lowering effects. Insulin secretagogues, biguanides, α-glucosidase inhibitors, thia zolidinediones, GLP-1RAs, DPP-4 inhibitors, SGLT-2 inhibitors, and insulin are approved for monotherapy of type 2 DM. Although each class of oral glucose-lowering agents has advantages and disadvantages (Table 416-6), certain generalizations apply: (1) insulin secretagogues, biguanides, GLP-1RAs, and thiazolidinediones improve glycemic con trol to a similar degree (1–2% reduction in HbA1c) and are more effective than α-glucosidase inhibitors, DPP-4 inhibitors, and SGLT-2

Individual with type 2 DM Develop person-centered, individualized plan • Medical nutrition therapy • Physical activity/lifestyle • Weight loss goal of 5–7% • Continue or initiate metformin Goal: Manage HbA1c + cardiorenal risk factor reduction Goal: Manage HbA1c + weight reduction or maintenance Heart failure, HFrEF, or HFpEF? CKD? ASCVD or ASCVD risk factors? GLP-1RA or SGLT-2 inhibitor SGLT-2 inhibitor SGLT-2 inhibitor HbA1c above target? HbA1c above target? • Add GLP-1RA • Add TZD • Add SGLT-2 inhibitor or GLP-1RA HbA1c above target? • Add insulin • Combination of injectable and oral • Re-emphasize lifestyle, nutrition, physical activity FIGURE 416-3 Glycemic management of type 2 diabetes. See text for discussion of treatment of severe hyperglycemia or symptomatic hyperglycemia. In this Figure, the term glucagon-like peptide-1 receptor agonists (GLP-1RAs) refers to GLP-1 RAs and dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RAs. Agents that can be combined with metformin include insulin, GLP-1RAs, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, insulin secretagogues, thiazolidinediones (TZD), α-glucosidase inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors. Injectable refers to insulin or GLP-RA. In individuals with type 2 DM and metabolic dysfunction–associated steatotic liver disease (see Chap. 354) or metabolic dysfunction–associated steatohepatitis (see Chap. 354), a GLP-1 RA or a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA and/or TZD (pioglitazone) should be considered. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction. inhibitors; (2) insulin secretagogues, GLP-1RAs, DPP-4 inhibitors, α-glucosidase inhibitors, and SGLT-2 inhibitors begin to lower the plasma glucose immediately, whereas the glucose-lowering effects of the biguanides and thiazolidinediones takes several days; (3) not all agents are effective in all individuals with type 2 DM; (4) biguanides, α-glucosidase inhibitors, GLP-1RAs, DPP-4 inhibitors, thiazolidinedio nes, and SGLT-2 inhibitors do not directly cause hypoglycemia; (5) 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; and (6) durability of glycemic control is slightly less for sulfonylureas compared to metformin or thiazolidinediones. COMBINATION THERAPY WITH GLUCOSE-LOWERING AGENTS The approach to type 2 DM has changed dramatically with the demon stration that GLP-1RAs and SGLT-2 inhibitors reduce cardiovascular events and slow the progression of renal disease, indicating that a GLP-1RA or an SGLT-2 inhibitor should be used in most individu als with type 2 DM. Therapy should be dictated by whether ASCVD, heart failure, or CKD is present or whether weight loss is a major goal (Fig. 416-3). A number of combinations of

therapeutic agents are use ful in type 2 DM: metformin plus SGLT-2 inhibitor, metformin plus GLP-1RA, metformin plus insulin, or combinations of a long-acting insulin and a GLP-1RA. Because the mechanism of action of the first and second agents differs, the effect on glycemic control is usually additive. Recent results from the National Institutes of Health–funded Glycemia Reduction Approaches in Diabetes: A Comparative Effec tiveness Study (GRADE) indicated that addition of liraglutide or basal

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CHAPTER 416 Weight loss Glycemia • GLP-1RA • Structured medical weight loss program • Metabolic surgery • GLP-1RA • GLP-1RA and insulin • Combination oral + injectable • Sulfonylurea • TZD • DPP-4 inhibitor insulin to metformin leads to better glycemic control than glimepiride or sitagliptin (SGLT-2 inhibitors were not studied). Medication costs vary considerably (Table 416-6), and this often factors into medication choice as drugs in some categories are very expensive (e.g., SGLT-2 inhibitors, GLP-1RAs). Several fixed-dose combinations of oral agents are available, but evidence that they are superior to titration of a single agent to a maximum dose and then addition of a second agent is lack ing. If adequate control is not achieved with the combination of two agents (based on reassessment of the HbA1c every 3 months), a third oral agent, including basal insulin, should be considered (Fig. 416-3). Treatment approaches vary considerably from country to country. For example, α-glucosidase inhibitors are used commonly in South Asian patients (Indian) but infrequently in the United States or Europe. Whether this reflects an underlying difference in the disease or physi cian preference is not clear. Treatment with insulin often becomes necessary as type 2 DM enters the phase of relative insulin deficiency and is signaled by inad equate glycemic control with one or two oral glucose-lowering agents. Insulin alone or in combination should be used in patients who fail to reach glycemic targets. For example, a single dose of long-acting insulin at bedtime is often effective in combination with metformin. As endogenous insulin production falls further, multiple injections of long-acting insulin together with rapid-acting insulin are necessary to control postprandial glucose excursions. These insulin regimens are identical to the long-acting and rapid-acting combination regimens discussed above for type 1 DM, although usually at higher doses given

insulin resistance. Weight gain and hypoglycemia are the major adverse effects of insulin therapy. The addition of a GLP-1RA can limit this and reduce the dose of insulin needed. The daily insulin dose required can become quite large (1–2 units/kg per day) as endogenous insulin production falls and insulin resistance persists, especially in the setting of weight gain. Insulin plus a thiazolidinedione promotes weight gain and may be associated with peripheral edema. Addition of a GLP-1RA or a thiazolidinedione may necessitate a reduction in the insulin dose to avoid hypoglycemia. Patients requiring large doses of insulin (>200 units/day) can be treated with more concentrated forms of insulin to reduce the volume of injectate and improve absorption.

PART 12 Endocrinology and Metabolism ■ ■OTHER THERAPIES FOR DIABETES Metabolic (also referred to as bariatric) surgery for obese individuals with type 2 DM has shown considerable effectiveness, sometimes with dramatic resolution of diabetes or major reductions in the needed dose of glucose-lowering therapies (Chaps. 413 and 414). Several large, nonrandomized clinical trials have demonstrated a much greater efficacy of metabolic surgery compared to medical management in the treatment of type 2 DM, but these trials were conducted before the advent of recently available GLP-1RAs. The ADA clinical guide lines state that metabolic surgery should be

considered in individuals with type 2 DM and a body mass index >30 kg/m2 if hyperglycemia is inadequately controlled despite optimal medical therapy. Metabolic surgery is ideally performed in certified centers with experience with the procedures and associated nutritional support. Short-term intense caloric restriction (very-low-calorie diet, typi cally 800–1000 calories/d) can dramatically improve type 2 DM, sometimes leading to resolution of the diabetes. Such an approach is more effective in recent-onset type 2 DM and should be supervised by a provider with expertise and accompanied by a long-term, weightmaintenance program. Whole-pancreas transplantation can normalize glucose control in type 1 DM and when performed simultaneously with or after kidney transplantation can prolong the life of the kidney transplant by offer ing protection against recurrent diabetic nephropathy. However, the number of whole-pancreas transplants is declining, likely reflecting the success with CGM and AID. Pancreatic islet transplantation is a less invasive form of beta-cell replacement therapy for type 1 DM; an islet product has received FDA approval. Despite the risks associated with chronic immunosuppression, whole-pancreas and pancreatic islet transplantation may be considered for patients with severe metabolic instability or already requiring immunosuppression in support of a kidney or other organ transplant. Patients with chronic pancreatitis and preserved islet function who require pancreatectomy for pain relief may benefit from autologous islet transplantation as this may prevent or ameliorate postsurgical DM. ■ ■EMERGING THERAPIES Recent clinical trials using transplantation of insulin-producing cells derived from human pluripotent stem cells have shown promise. Cost, durability, long-term safety, and patient selection remain to be determined. Many individuals with long-standing type 1 DM still produce very small amounts of insulin or have insulin-positive cells within the pancreas. This suggests that beta cells may slowly regen erate but are quickly destroyed by the autoimmune process. Efforts to suppress the autoimmune process, for example, with a monoclo nal antibody that targets T lymphocytes, may preserve beta cells when given at the time of new-onset hyperglycemia in type 1 DM. This agent, teplizumab, a humanized monoclonal antibody to CD3 on T cells, has been approved by the FDA to delay the onset of clinical type 1 DM (stage 3) in patients 8 years of age or older with preclinical (stage 2) disease. Agents that target thioredoxin-interacting protein (TXNIP), especially Ca2+ channel blockers, have shown promise in recent-onset type 1 DM and in rodent models of diabetes. ADVERSE EFFECTS OF THERAPY FOR DM The benefits of efforts directed toward glycemic control must be bal anced against the risks of treatment (Table 416-6). Side effects of inten sive treatment include an increased frequency of serious hypoglycemia,

weight gain, and greater demands on the individual with diabetes. The most serious complication of therapy for DM is hypoglycemia, and its prevention and treatment with oral glucose or glucagon administered intra-nasally or by injection are discussed in Chap. 418. Severe, recur rent, or unexplained hypoglycemia warrants reassessment of the treat ment regimen and glycemic goal for the individual patient and possibly deintensification of insulin therapy (see categories of individuals for this would be appropriate in Table 416-4). Weight gain occurs with most (insulin, insulin secretagogues, thiazolidinediones) but not all (metformin, α-glucosidase inhibitors, GLP-1RAs, SGLT-1 inhibitors, DPP-4 inhibitors) therapies. The weight gain is partially due to the anabolic effects of insulin and the reduction in glucosuria. ACUTE DISORDERS RELATED TO SEVERE HYPERGLYCEMIA Individuals with type 1 or type 2 DM and severe hyperglycemia should be assessed for clinical stability, including mentation and hydration. The physician should determine if the individual with diabetes is stable or if DKA or a hyperglycemic hyperosmolar state (HHS) is present. In DKA, the hyperglycemia is accompanied by increased ketone concentration in blood

and metabolic acidosis. In HHS, the hyperglycemia is usually greater, leading to hyperosmolality and marked dehydration but with out ketosis or acidosis. Ketones bodies, an indicator of DKA, should be measured in individuals with type 1 DM when the plasma glucose is persistently >13.9 mmol/L (250 mg/dL). The possibility of DKA should always be considered in patients with type 1 DM during a concurrent illness or with symptoms such as nausea, vomiting, or abdominal pain. Measurement of β-hydroxybutyrate in the blood is preferred over urine testing with nitroprusside-based assays that measure only acetoacetate and acetone. Worldwide, the number of reported cases of DKA and HHS is increasing for unclear reasons. Both DKA and HHS are associ ated with potentially serious complications, including greater mortality. Most cases of DKA are in individuals with type 1 DM, while HHS occurs mostly in individuals with type 2 DM. DKA, formerly consid ered a hallmark of type 1 DM, can also occur at diabetes diagnosis in obese young adults, often of Hispanic or African descent, whose labo ratory values are similar to those seen in DKA associated with type 1 DM. However, after treatment of the DKA, these individuals recover their insulin secretory capacity, can gradually discontinue insulin treat ment after a few weeks or months, and remain normoglycemic with only diet or oral medication. The cause of this atypical form of diabetes is unknown; it is often termed ketosis-prone diabetes. DKA can also occur in the setting of treatment of type 2 DM with an SGLT-2 inhibi tor. Often the blood glucose is normal or just mildly elevated because of the glucosuria. Table 416-7 compares the features of DKA, HHS, and euglycemic DKA associated with SGLT-2 inhibitors. DKA and HHS exist along a continuum of hyperglycemia, with up to one-third of patients having features of both. ■ ■DIABETIC KETOACIDOSIS Clinical Features The symptoms and physical signs of DKA are listed in Table 416-8 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 aci dosis 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 (e.g., infection, hypoxemia). 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. Failure to augment insulin therapy during physiologic stress often compounds

TABLE 416-7 Laboratory Values in Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), and Euglycemic DKA [Representative Ranges at Presentation; mmol/L (mg/dL)] DKA HHS EUGLYCEMIC DKAc Glucose,a mmol/L (mg/dL) 11.1–33.3 (250–600) 33.3–66.6 (600–1200) 5.5-13.9 (100–250)c Sodium, meq/L 125–135 135–145 Normal Potassiuma,b Normal to ↑ Normal Normal to ↑ Magnesiuma Normal Normal Normal Chloridea Normal Normal Normal Phosphatea,b Normal Normal Normal Creatinine Slightly to moderately ↑ Moderately ↑ Slightly ↑ Osmolality (mOsm/mL)

> 300 300 Normal Serum/urine ketonesa ++ +/– ++ Serum β-hydroxybutyrate, mmol/L 3.0 <1.0 3.0 Serum bicarbonate,a meq/L <18 18 <18 Arterial pH 6.8–7.3

7.3 <7.3 Arterial Pco2,a mmHg 20–30 Normal 20–30 Anion gapa (Na – [Cl + HCO3]) ↑ Normal to slightly ↑ ↑ aLarge changes occur during treatment of DKA; serum level may be normal initially but then require replacement. bAlthough plasma levels may be normal or high at presentation, total-body stores are usually depleted. cSometimes occurs with sodium-glucose cotransporter 2 (SGLT-2) inhibitor treatment; disproportionate glucosuria is consistent with SGLT-2 inhibitor effect. the problem. Tissue ischemia (heart, brain) can also be a precipitating factor. Omission of insulin because of an infusion pump delivery site occlusion or device malfunction, eating disorder, mental health disor ders, or an unstable psychosocial environment may each be a factor precipitating DKA. Complete omission or inadequate administration of insulin by the patient or health care team (in a hospitalized patient with type 1 DM) may precipitate DKA. The rising cost of insulin has been a major challenge and has contributed to individuals with diabetes omit ting or rationing their insulin, making them more vulnerable to DKA. Pathophysiology DKA results from relative or absolute insulin deficiency combined with counterregulatory hormone excess (gluca gon, catecholamines, cortisol, and growth hormone). 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. 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 cate cholamines and growth hormone, also increase lipolysis and the release of free fatty acids. Markers of inflammation (cytokines, C-reactive protein) are elevated in both DKA and HHS. Laboratory Abnormalities and Diagnosis The timely diag nosis of DKA is crucial and allows for prompt initiation of therapy. DKA is characterized by hyperglycemia (serum glucose >13.9 mmol/L [250 mg/dL], ketosis, and metabolic acidosis [serum bicarbonate <15–18 mmol/L with increased anion gap]) along with a number of TABLE 416-8 Manifestations of Diabetic Ketoacidosis Symptoms Nausea/vomiting Thirst/polyuria Abdominal pain Shortness of breath Precipitating events Inadequate insulin administration Infection (pneumonia/UTI/ Physical Findings Tachycardia Dehydration/hypotension Tachypnea/Kussmaul respirations/ respiratory distress Abdominal tenderness (may resemble acute pancreatitis or surgical abdomen) Lethargy/obtundation/cerebral gastroenteritis/sepsis) Infarction (cerebral, coronary, edema/possibly coma mesenteric, peripheral) Pancreatitis Drugs (cocaine) Pregnancy Abbreviation: UTI, urinary tract infection.

 secondary metabolic derangements (Table 416-7). Occasionally, the serum glucose is only minimally elevated and may even be normal (euglycemic DKA). This has been noted especially in individuals treated with SGLT-2 inhibitors. Arterial pH usually 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 and volume

depletion. Total-body stores of sodium, chloride, phosphorus, and magnesium are also reduced in DKA but are not accurately reflected by their levels in the serum because of hypovolemia and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Leukocytosis, hypertriglyceridemia, and hyperli poproteinemia 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. An estimated correction is provided by the equa tion: (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 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). The nitroprusside tablet, or stick, is often used to detect urine ketones; certain medications such as captopril, penicil lamine, or valproic acid may cause false-positive reactions. Serum or plasma assays for β-hydroxybutyrate are preferred because they more accurately reflect the true ketone body level. The degree of acidosis and hyperglycemia do not necessarily cor relate closely because a variety of factors determine the level of hyper glycemia (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 forms of increased anion-gap acidosis (Chap. 55). TREATMENT Diabetic Ketoacidosis Based on laboratory values and clinical exam, DKA can be classified as mild (pH 7.25–7.3, serum bicarbonate 15–18 meq/L, men tal status normal), moderate (pH 7.0–7.25, serum bicarbonate 10–15 meq/L, mildly reduced mental status), or severe (pH <7.0,

serum bicarbonate <10–15 meq/L, reduced mental status, coma). The management of DKA is outlined in Table 416-9. After initiat ing IV fluid replacement and insulin therapy, the event that precipi tated the episode of DKA should be sought and aggressively treated. If the patient is vomiting or has altered mental status, a nasogastric tube should be inserted to prevent aspiration of gastric contents. Central to successful treatment of DKA is careful monitoring and frequent reassessment to ensure that the patient and the metabolic derangements are improving. A comprehensive flow sheet should record chronologic changes in vital signs, fluid intake and output, and laboratory values as a function of insulin administered.

After the initial bolus of normal saline or lactated Ringer’s, 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 or lactated Ringer’s, depending on the calculated volume deficit. Ringer’s lactate is associated with more rapid DKA resolution and a reduced trend toward hyperchloremia later in the course of DKA resolution. PART 12 Endocrinology and Metabolism A bolus of IV (0.1 units/kg) short-acting regular insulin is usu ally administered immediately (Table 416-9), and subsequent treat ment should provide continuous and adequate levels of circulating TABLE 416-9 Management of Diabetic Ketoacidosis (DKA)

1. Confirm diagnosis (↑ serum glucose, ↑ serum β-hydroxybutyrate, metabolic acidosis).

2. Admit to hospital; intensive care setting may be necessary for severe DKA (see text). Mild to moderate DKA can be treated in a step-down unit with close nursing and laboratory monitoring.
3. Assess: Serum electrolytes (K+, Na+, Mg2+, Cl–, bicarbonate, phosphate) Acid-base status—pH, HCO3 –, PCO2, β-hydroxybutyrate Renal function (creatinine, urine output)
4. Replace fluids: 2–3 L of 0.9% saline or lactated Ringer's over first 1–3 h (10–20 mL/kg per hour); subsequently, 0.45% saline at 250–500 mL/h; change to 5–10% glucose and 0.45% saline or lactated Ringer's at 150–250 mL/h when blood glucose reaches 250 mg/dL (13.9 mmol/L). For treatment of euglycemic DKA, start 5% or 10% dextrose infusion and insulin treatment when 0.9% saline is started; adjust dextrose infusion to prevent hypoglycemia.
5. Administer short-acting regular insulin: IV (0.1 units/kg), then 0.1 units/ kg per hour by continuous IV infusion; increase two- to threefold if no response by 2–4 h. In mild to moderate DKA, subcutaneous rapid-acting insulin may be used with close monitoring (0.1 unit/kg rapid-acting insulin analogue subcutaneously and then 0.1 unit/kg every 1 h or 0.2 unit/kg every 2 h). Continue insulin treatment and 5% or 10% dextrose infusion to prevent hypoglycemia. If the initial serum potassium is <3.3 mmol/L (3.3 meq/L), do not administer insulin until the potassium is corrected.
6. Assess patient: What precipitated the episode (noncompliance, infection, trauma, pregnancy, infarction, cocaine)? Initiate appropriate workup for precipitating event (cultures, CXR, ECG, etc.).
7. Measure blood 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+ if ECG, urine flow, and creatinine are normal. If K+ <3.5 mmol/L, administer 10–20 mmol/L per hour until K+ >3.5 mmol/L. If K+ 3.5–5 mmol/L, administer 10–20 mmol/L in each liter of IV fluid to keep serum K+ between 4 and 5 mmol/L. If K+ >5.0 mmol/L, start insulin but hold K+. Recheck K+ every 2 h to determine when to start K+ replacement.
10. Continue above until patient is stable, glucose goal is 8.3–11.1 mmol/L (150–200 mg/dL), normal plasma ketone and pH, and bicarbonate ≥18 mmol/L. Insulin infusion may be decreased to 0.02–0.1 unit/kg per hour. Resolution of euglycemic DKA should be based on bicarbonate, not glucose, correction; see text.
11. Administer long-acting insulin as soon as patient is eating. Allow for a 2- to 4-h overlap in insulin infusion and SC long-acting insulin injection. Abbreviations: CXR, chest x-ray; ECG, electrocardiogram. Source: Adapted from multiple sources, including Nyenwe EA, Kitabchi AE: The evolution of diabetic ketoacidosis: An update of its etiology, pathogenesis and management. Metabolism 65:507, 2016; and Umpierrez GE et al: Hyperglycaemic crises in adults with diabetes: A consensus report. Diabetologia 67:1455, 2024.

insulin. IV administration is usually preferred (0.1 units/kg of regu lar insulin per h) but uncomplicated DKA can also be treated with SC short-acting insulin analogues. As the acidosis and insulin resis tance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.02–0.1 units/kg per h). Long-acting insulin, in combination with SC short-acting insulin, should be administered as soon as the patient resumes eating, because this facilitates transi tion to an outpatient insulin regimen and reduces length of hospital stay. Hyperglycemia usually improves at

a rate of 4.2–5.6 mmol/L (50–100 mg/dL) per h as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. Rehy dration 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. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral ketone body use, sup presses hepatic ketone body formation, and promotes bicarbonate regeneration. However, the acidosis and ketosis resolve more slowly than hyperglycemia. Depending on the rise of serum chloride, the anion gap (but not bicarbonate) will normalize more quickly. 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 excrete 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 hypokale mia. 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 (Table 416-9). Bicarbonate replacement has not been shown to improve out comes. However, in the presence of severe acidosis (arterial pH <7.0), sodium bicarbonate (50 mmol [meq/L] in 200 mL of sterile water with 10 meq/L KCl per h) may be administered for the first 2 h until the pH is >7.0. Hypophosphatemia and hypomagnesemia may develop during DKA therapy, and if severe, may also require supplementation. With appropriate therapy, the mortality rate of DKA is low (<1%) and is related more to the underlying or precipitating event, such as infection ((pneumonia, SARS-Co-V2, etc.) COVID-19), pregnancy, end-stage renal disease, or myocardial infarction. Venous throm bosis, upper GI bleeding, and acute respiratory distress syndrome occasionally complicate DKA. The major nonmetabolic complica tion of DKA therapy is cerebral edema, which most often devel ops in children as DKA is resolving. The etiology of and optimal therapy for cerebral edema are not well established. Following treatment, the physician and patient should review the sequence of events that led to DKA to prevent future recurrences. Even a single episode of DKA is associated with a greatly increased 1-year mortality rate. Foremost is patient education about the symptoms of DKA, its precipitating factors, and the management of diabetes during a concurrent illness. In some individuals, DKA is recurrent and may indicate underlying mental health issues. The structural barriers to accessing care, insulin cost, and the social determinants of health often play a role. ■ ■HYPERGLYCEMIC HYPEROSMOLAR STATE Clinical Features The most common presentation of 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, concur rent 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 gluconeogen esis) and impairs glucose utilization in skeletal muscle (see above dis cussion 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 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 fea tures in HHS are summarized in Table 416-7. Most notable are the marked hyperglycemia (plasma glucose may be >55.5 mmol/L [1000 mg/dL]), hyperosmolality (>300 mOsm/L), and prerenal azo temia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased (add 1.6 meq to measured sodium for each 5.6-mmol/L [100-mg/dL] rise in the serum glucose). In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion-gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation. TREATMENT Hyperglycemic Hyperosmolar State Volume depletion and hyperglycemia are prominent features of both HHS and DKA. Consequently, the therapy of these disorders shares several elements (Table 416-9). In both disorders, careful monitoring of the patient’s fluid status, laboratory values, and insu lin 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 comorbidi ties. Even with proper treatment, HHS has a substantially higher mortality rate 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 is >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 [D5W]). The calculated free water deficit (which can be as great as 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 usu ally 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 KPO4 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 unit/kg followed by IV insulin at a constant infusion rate of 0.1 unit/kg per h. 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 11.1–13.9 mmol/L (200–250 mg/dL), and the insulin infusion rate should be decreased to 0.02–0.1 unit/kg per h. The insulin infusion should be continued until the patient has resumed eating and can be transferred to an SC insulin regi men. The patient should be discharged from the hospital on insulin. Some patients can later switch to oral glucose-lowering agents.

MANAGEMENT OF DIABETES IN A HOSPITAL OR FACILITY Virtually all medical and surgical subspecialties are involved in the care of hospitalized patients with diabetes or individuals with

diabetes in the perioperative setting. 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 counter regulatory 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, thus, may promote hypoglycemia. Glycemic control should be assessed on admission using the HbA1c. Electrolytes, renal function, and intravascular volume status should be assessed as well. The high prevalence of ASCVD in individuals with DM (especially in type 2 DM) may necessitate pre operative cardiovascular evaluation (Chap. 417). CGM in the hospital or intensive care unit (ICU) setting is not FDA approved. Individuals using CGM and/or AID prior to admission should continue to use these devices if the provider, the nursing staff, and the patient agree that this can be safely done within the context of the patient's current reason for hospitalization. Diabetes Mellitus: Management and Therapies

CHAPTER 416 The goals of diabetes management during hospitalization or in the perioperative periods are near-normoglycemia, avoidance of hypogly cemia, and transition back to the outpatient diabetes treatment regi men. Upon hospital admission, frequent glycemic monitoring should begin, as should planning for diabetes management after discharge. Glycemic control appears to improve clinical outcomes in a variety of settings, but optimal glycemic goals for the hospitalized patient are incompletely defined. 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. In some studies, 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. How ever, a large randomized clinical trial (Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation [NICESUGAR]) of individuals in the ICU (most of whom were receiving mechanical ventilation) found an increased mortality rate and a greater number of episodes of severe hypoglycemia with very strict glycemic control (target blood glucose of 4.5–6 mmol/L or 81–108 mg/dL) com pared to individuals with a more moderate glycemic goal (target blood glucose of <10 mmol/L or 180 mg/dL). Currently, most data suggest that very strict blood glucose control in acutely ill patients likely wors ens outcomes and increases the frequency of hypoglycemia. The ADA suggests the following glycemic goals for hospitalized patients: (1) in critically or non-critically ill patients, glucose of 7.8–10.0 mmol/L or 140–180 mg/dL; (2) in selected patients, glucose of 6.1–7.8 mmol/L or 110–140 mg/dL with avoidance of hypoglycemia; and (3) the target range in the perioperative period should be 80–180 mg/dL (4.4–10.0 mmol/L). Critical aspects for optimal diabetes care in the hospital include the following: (1) A hospital-wide system approach to treatment of hyper glycemia and prevention of hypoglycemia is needed. Inpatient diabetes management teams consisting of nurse practitioners and physicians are increasingly common. (2) Diabetes treatment plans should focus on the transition from the ICU and the transition from the inpatient to the outpatient setting. (3) Adjustment of the discharge treatment

regimen of patients whose diabetes was poorly controlled on admission (as reflected by the HbA1c) is important.

The physician caring for an individual with diabetes in the peri operative period, during times of infection or serious physical illness, or simply when the patient is fasting for a diagnostic procedure must monitor the plasma glucose vigilantly, adjust the diabetes treatment regimen, and provide glucose infusion as needed. Hypoglycemia is frequent in hospitalized patients, and many of these episodes are avoid able. Hospital systems should have a diabetes management protocol to avoid inpatient hypoglycemia. Measures to reduce or prevent hypogly cemia include frequent glucose monitoring, but it is also important to prevent hypoglycemia by anticipating drops in insulin requirement by factors such as decreasing renal function, decreasing glucocorticoid doses, or interruption of nutrition (parenteral or enteral or PO). PART 12 Endocrinology and Metabolism Depending on the severity of the patient's illness and the hospital setting, the physician can use either an insulin infusion or SC insulin. Insulin infusions are preferred in the ICU or in a clinically unstable setting because the half-life of the infused insulin is quite short (minutes). The absorption of SC insulin may be variable in such situations. Insu lin infusions can also effectively control plasma glucose in the peri operative period and when the patient is unable to take anything by mouth, although for relatively short (<4 h) procedures, most patients can remain on SC insulin. Regular insulin is used rather than insulin analogues for IV insulin infusion because it is less expensive and equally effective. The physician must consider carefully the clinical setting in which an insulin infusion will be used, including whether adequate ancillary personnel are available to monitor the blood glucose frequently and whether they can adjust the insulin infusion rate to maintain the blood glucose within the optimal range. Insulin-infusion algorithms should integrate the insulin sensitivity of the patient, fre quent blood glucose monitoring, and the trend of changes in the blood glucose to determine the insulin-infusion rate. Insulin-infusion algo rithms jointly developed and implemented by nursing and physician staff are advised. 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 (2–4 h before the infusion is stopped) to avoid a period of insulin deficiency. In patients who are not critically ill or not in the ICU, basal or "scheduled" insulin is provided by SC, long-acting insulin supple mented by prandial and/or "corrective" insulin using a rapid-acting insulin. "Sliding scale," with short-acting or rapid-acting insulin alone, where no insulin is given unless the blood glucose is elevated, is inad equate for inpatient glucose management. The rapid-acting, prepran dial insulin dose should include coverage for food consumption (based on anticipated carbohydrate intake) plus corrective insulin based on the patient's insulin sensitivity and the blood glucose. For example, if the patient is thin (and likely insulin-sensitive), an insulin correction factor might be 1 unit for each 2.7 mmol/L (50 mg/dL) over the glucose target. If the patient is obese and likely insulin-resistant, then the insu lin correction factor 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 and prandial insulin doses frequently based on the corrective insulin required. A consistent carbohydrate-controlled diabetes meal plan for hospitalized patients provides a predictable amount of carbohydrate for a particular meal each day (but not neces sarily the same amount for breakfast, lunch, and supper) and avoids concentrated sweets. Individuals with type 1 DM who are undergoing general anesthesia and surgery or who are seriously ill should receive continuous insulin, through an IV insulin infusion, their insulin infu sion device, or by SC administration of a reduced dose of long-acting insulin. Rapid-acting insulin alone is insufficient. Prolongation of a surgical procedure or delay in the recovery room is common and may result in periods of insulin deficiency leading to DKA. Insulin infusion is the preferred method for managing patients with type

1 DM over a prolonged (several hours) perioperative period or when serious con current illness is present (0.5–1.0 units/h of regular insulin). If the diag nostic or surgical procedure is brief (<4 h), a reduced dose of SC insulin may suffice (20–50% basal reduction, with rapid-acting correctional dose insulin as needed). This approach prevents interruption of insulin

infusion device therapy or, for MDI, facilitates the transition back to basal/bolus insulin after the procedure. 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 an insulin infusion or SC long-acting insulin (20–50% reduction depending on clinical setting) plus preprandial, rapid-acting insulin. Oral glucoselowering agents should be discontinued upon admission (or up to a week prior to planned admission for SGLT-2 inhibitors) and 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, euglycemic DKA with SGLT-2 inhibitors) or at risk for declining kidney function due to, for example, radiographic contrast media or unstable CHF (lactic acidosis with metformin). Once clinically stable, oral glucose-lowering agents may be resumed in anticipation of discharge. Each patient should receive an individualized, structured discharge plan for diabetes management. The principles of the care of individuals with diabetes who are in a rehabilitation facility or a long-term care facility are similar to those in a hospitalized patient with the glycemic goals individualized based on the patient’s overall clinical status (outlined in Table 416-4). Often the avoidance of hypoglycemia is the major goal with less intense glycemic targets. SPECIAL CONSIDERATIONS IN DM ■ ■TOTAL PARENTERAL NUTRITION (TPN)/TOTAL ENTERAL NUTRITION (TEN) (See also Chap. 335) TPN or TEN greatly increases insulin require ments. In addition, individuals not previously known to have DM may become hyperglycemic during TPN or TEN and require insulin treatment. For TPN, IV 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, a proportion of this insulin may be added directly to the TPN solution to cover the nutritional requirements for insulin and adjusted based on the need for modified dosing of rapidacting insulin. In TEN, hyperglycemia may be limited by using highprotein formulations but often requires insulin treatment. Individuals receiving enteral bolus feedings should receive SC, rapid-acting insulin prior to each bolus. As a start, 1 unit of insulin is given SC for each 10–15 g of carbohydrate in the bolus. Patients with insulin deficiency (type 1 DM and pancreatogenic DM) should also receive long-acting insulin (0.1–0.2 units/kg per day) to cover basal insulin requirements should the TPN or TEN be interrupted or cycled. ■ ■GLUCOCORTICOIDS Glucocorticoids increase insulin resistance, decrease glucose utiliza tion, increase hepatic glucose production, and impair insulin secretion. These changes lead to a worsening of glycemic control in individuals with DM and may precipitate hyperglycemia in other individuals. If new-onset hyperglycemia remains during chronic treatment with supraphysiologic doses of glucocorticoid (>5 mg of prednisone or equivalent), the DM may be called “steroid-induced diabetes.” The effects of glucocorticoids on glucose homeostasis are dose-related, usually reversible, most pronounced in the postprandial period, and dependent on the timing and type of glucocorticoid. If the FPG is near the normal range, oral diabetes agents (e.g., sulfonylureas, metformin) may be sufficient to reduce hyperglycemia. If the FPG is >11.1 mmol/L (200 mg/dL), oral agents are usually not sufficient, and insulin therapy is required. If steroids are administered in the morning, then shortacting insulin and/or NPH in the morning may be sufficient to control postprandial glucose excursions. ■ ■DIABETES MANAGEMENT IN OLDER ADULTS Diabetes is very common in older adults, being present in ~25% of individuals over the age of 65 years. Increasingly, individuals with many years

of type 1 DM are part of this patient population. As discussed above (Table 416-4), individualized therapeutic goals and modalities in older adults should consider biologic age, other

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