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Pneumonia, urinary tract infections, and skin and soft tissue infec tions are all more common in the diabetic population. In general, the organisms that cause pulmonary infections are similar to those found in the nondiabetic population; however, gram-negative organ isms, S. aureus, and Mycobacterium tuberculosis are more frequent pathogens. Adults with DM should receive vaccination against pneu mococcus, respiratory syncytial virus, annually against influenza, and the coronavirus SARS-CoV-2, which causes increased morbidity and mortality in obese individuals and patients with DM (Chap. 204). In addition to early antibiotic therapy for presumed bacterial infections, patients with DM should be considered for early intervention with antiviral agents (e.g., against influenza in flu, varicella-zoster virus in shingles) or SARS-CoV-2 in COVID. Urinary tract infections (either lower tract or pyelonephritis) are the result of common bacterial agents such as Escherichia coli, although several yeast species (e.g., Candida albicans and C. glabrata) are sometimes observed. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Bacteriuria occurs frequently in individuals with diabetic cystopathy and does not require antibiotic therapy except in specific circumstances such as pregnancy or a planned urologic pro cedure. Susceptibility to furunculosis, superficial candidal infections, and vulvovaginitis are increased. Poor glycemic control is a common denominator in individuals with these infections. Individuals with diabetes have an increased rate of colonization of S. aureus in the skinfolds and nares. Individuals with diabetes also have a greater risk of postoperative wound infections that may be mitigated by periopera tive protocols for insulin administration to maintain glycemic control.

PART 12 Endocrinology and Metabolism ■ ■DERMATOLOGIC MANIFESTATIONS The most common skin manifestations of DM are xerosis and pruritus and are usually relieved by skin moisturizers. Protracted wound heal ing and skin ulcerations are also frequent complications. Diabetic der mopathy, sometimes termed pigmented pretibial papules, or “diabetic skin spots,” begins as an erythematous macule or papule that evolves into an area of circular hyperpigmentation. These lesions result from minor mechanical trauma in the pretibial region and are more com mon in elderly men with DM. Bullous diseases, such as bullosa dia beticorum (shallow ulcerations or erosions in the pretibial region), are also seen. Necrobiosis lipoidica diabeticorum is an uncommon disorder, accompanying diabetes in predominantly young women. This usually begins in the pretibial region as an erythematous plaque or papules that gradually enlarge, darken, and develop irregular margins, with atrophic centers and central ulceration. They are often painful. Vitiligo and alopecia areata occur at increased frequency in individuals with type 1 DM. Acanthosis nigricans (hyperpigmented velvety plaques seen on the neck, axilla, or extensor surfaces) is sometimes a feature of severe insulin resistance and accompanying diabetes. Generalized or local ized granuloma annulare (erythematous plaques on the extremities or trunk), lichen planus (violaceous

papules on the cutaneous surface with or without erosions in the mouth and genitalia), and scleredema (areas of skin thickening on the back or neck at the site of previous superficial infections) are more common in the diabetic population. Lipoatrophy and lipohypertrophy can occur at insulin injection sites but are now unusual with the use of human insulin and avoided by rotating injection sites. ■ ■FURTHER READING Abel ED et al: Diabetes mellitus-progress and opportunities in the evolving epidemic. Cell 187:3789, 2024. Adler AI et al: Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). Lancet 404:145, 2024. American Diabetes Association: Cardiovascular disease and risk management: Standards of Medical Care in Diabetes-2024. Diabetes Care 47:S179, 2024. American Diabetes Association: Chronic kidney disease and risk management: Standards of Care in Diabetes—2024. Diabetes Care 47:S219, 2024.

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Hypoglycemia Hypoglycemia is most commonly caused by insulin or insulin-producing drugs used to treat diabetes mellitus or by exposure to other drugs, including alcohol. However, a number of other disorders, including critical organ failure, sepsis and inanition, hormone deficiencies, nonβ-cell tumors, insulinoma, inborn errors of metabolism, and prior gastric surgery, can cause hypoglycemia (Table 418-1). Hypoglycemia may be documented by Whipple’s triad: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration measured with a precise method, and (3) relief of symptoms after the plasma glucose level is raised. The lower limit of the fasting plasma glucose concentra tion is normally ~70 mg/dL (~3.9 mmol/L), but lower venous glucose levels occur normally, late after a meal, during pregnancy, and during prolonged fasting (>24 h). Severe hypoglycemia can cause serious morbidity and increase the risk for serious cardiovascular events and mortality during and after the initial hypoglycemic episode. It should be considered in any patient with episodes of confusion, an altered level of consciousness, or a seizure. ■ ■SYSTEMIC GLUCOSE BALANCE AND GLUCOSE COUNTERREGULATION Glucose is an obligate metabolic fuel for the brain under physiologic conditions. The brain cannot synthesize glucose or store more than a few minutes’ supply as glycogen and therefore requires a continuous supply of glucose from the arterial circulation. As the arterial plasma glucose concentration falls below the physiologic range, blood-to-brain glucose transport becomes insufficient to support brain energy metab olism and function. However, multiple integrated glucose counterregu latory

mechanisms normally prevent or rapidly correct hypoglycemia. Plasma glucose concentrations are normally maintained within a relatively narrow range—roughly 70–110 mg/dL (3.9–6.1 mmol/L) in the fasting state, with transient higher excursions after a meal— despite wide variations in exogenous glucose delivery from meals and in endogenous glucose utilization by, for example, exercising muscle. Between meals and during fasting, plasma glucose levels are maintained

TABLE 418-1 Causes of Hypoglycemia Across the Life Span Ill or Medicated Individual 1. Drugs Insulin or insulin secretagogues Alcohol Others 2. Critical illness Hepatic, renal, or cardiac failure Sepsis Inanition 3. Hormone deficiency Cortisol Growth hormone Glucagon and epinephrine (in insulin-deficient diabetes) 4. Non–islet cell tumor (e.g., mesenchymal tumors) Seemingly Well Individual 5. Endogenous hyperinsulinism Insulinoma Functional β-cell disorders (nesidioblastosis) Noninsulinoma pancreatogenous hypoglycemia Post–gastric bypass hypoglycemia Insulin autoimmune hypoglycemia Antibody to insulin Antibody to insulin receptor GLP-1 receptor agonists in combination with insulin and/or insulin secretagogues Insulin secretagogues Other 6. Disorders of gluconeogenesis and fatty acid oxidation 7. Exercise 8. Accidental, surreptitious, or malicious hypoglycemia 9. Prolonged fasting 10. Pregnancy Source: Reproduced with permission from PE Cryer et al: Evaluation and management of adult hypoglycemic disorders: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 94:709, 2009. Arterial glucose Pancreas Brain Glucagon Sympathoadrenal outflow Pituitary Adrenal medullae Epinephrine Growth hormone Sympathetic postganglionic neurons (ACTH) Adrenal cortex Norepinephrine Acetylcholine Cortisol FIGURE 418-1 Physiology of glucose counterregulation: Mechanisms that normally prevent or rapidly correct hypoglycemia. In insulin-deficient diabetes, the key counterregulatory responses—suppression of insulin and increases in glucagon—are lost, and stimulation of sympathoadrenal outflow is attenuated. ACTH, adrenocorticotropic hormone.

by endogenous glucose production, hepatic glycogenolysis, and hepatic (and renal) gluconeogenesis (Fig. 418-1). Although hepatic glycogen stores are usually sufficient to maintain plasma glucose levels for ~8 h, this period can be shorter if glucose demand is increased by exercise or if glycogen stores are depleted by illness or starvation.

Gluconeogenesis normally requires low insulin levels and the pres ence of anti-insulin (counterregulatory) hormones together with a coordinated supply of precursors from muscle and adipose tissue to the liver and kidneys. Muscle provides lactate, pyruvate, alanine, gluta mine, and other amino acids. Triglycerides in adipose tissue are broken down into fatty acids and glycerol, which is a gluconeogenic precursor. Fatty acids provide an alternative oxidative fuel to tissues other than the brain (which requires glucose). Hypoglycemia CHAPTER 418 Systemic glucose balance, maintenance of the normal plasma glucose concentration, is accomplished by a network of hormones, neural signals, and substrate effects that regulate endogenous glucose production and glucose utilization by tissues other than the brain

(Chap. 415). Among the regulatory factors, insulin plays a dominant role (Table 418-2; Fig. 418-1). As plasma glucose levels decline within the physiologic range, pancreatic β-cell insulin secretion decreases, thereby increasing hepatic glycogenolysis and hepatic (and renal) gluconeogenesis. Low insulin levels also reduce glucose utilization in peripheral tissues, inducing lipolysis and proteolysis and consequently releasing gluconeogenic precursors. Thus, a decrease in insulin secre tion is the first defense against hypoglycemia. As plasma glucose levels decline just below

the physiologic range, glucose counterregulatory (plasma glucose–raising) hormones are released (Table 418-2; Fig. 418-1). Among these, pancreatic α-cell glu cagon and adrenomedullary epinephrine play a primary role. Glucagon stimulates hepatic glycogenolysis and gluconeogenesis. Adrenomedul lary epinephrine also stimulates hepatic glycogenolysis and gluconeo genesis (and renal gluconeogenesis) but limits peripheral uptake of glucose and stimulates lipolysis with production of glycerol and fatty acids. Epinephrine becomes critical when glucagon is deficient. When hypoglycemia is prolonged beyond ~4 h, cortisol and growth hormone also support glucose production and restrict glucose utilization to a limited amount (both mechanisms are reduced by ~80% compared to epinephrine). Thus, cortisol and growth hormone play no role in defense against acute hypoglycemia. Liver Insulin Kidneys Glucose production Arterial glucose Fat Muscle Gluconeogenic precursor (lactate, amino acids, glycerol) Glucose clearance (Ingestion) Symptoms

TABLE 418-2 Physiologic Responses to Decreasing Plasma Glucose Concentrations GLYCEMIC THRESHOLD,

mmoL/L (mg/dL) PHYSIOLOGIC ↓ EFFECTS RESPONSE ↓ Insulin 4.4–4.7 (80–85) ↑ Ra (↓ Rd), increased lipolysis; ↑ FFA

↑ Glycerol ↑ Glucagon 3.6–3.9 (65–70) ↑ Ra Primary glucose counterregulatory factor/second defense against hypoglycemia ↑ Epinephrine 3.6–3.9 (65–70) ↑ Ra, ↓ Rc, increased lipolysis;

↑ FFA and glycerol 3.6–3.9 (65–70) ↑ Ra, ↓ Rc Involved in defense against prolonged hypoglycemia;

not critical ↑ Cortisol and growth hormone PART 12 Endocrinology and Metabolism Symptoms 2.8–3.1 (50–55) Recognition of hypoglycemia Prompt behavioral defense against hypoglycemia

(food ingestion) ↓ Cognition <2.8 (<50) — Compromises behavioral defense against hypoglycemia Note: Ra, rate of glucose appearance, glucose production by the liver and kidneys; Rc, rate of glucose clearance, glucose utilization relative to the ambient plasma glucose by insulin-sensitive tissues; Rd, rate of glucose disappearance, glucose utilization by insulin-sensitive tissues such as skeletal muscle. Rd by the brain is not altered by insulin, glucagon, epinephrine, cortisol, or growth hormone. Abbreviation: FFA, free fatty acids. Source: Reproduced with permission from PE Cryer, in S Melmed et al: Williams Textbook of Endocrinology, 12th ed. New York, NY: Elsevier; 2012. As plasma glucose levels fall further, symptoms prompt behavioral defense against hypoglycemia, including the ingestion of food (Table 418-2; Fig. 418-1). The normal glycemic thresholds for these responses to decreasing plasma glucose concentrations are shown in Table 418-2. However, these thresholds are dynamic. They shift to higher-thannormal glucose levels in people with poorly controlled diabetes, who can experience symptoms of hypoglycemia when their glucose levels decline toward the normal range. On the other hand, thresholds shift to lower-than-normal glucose levels in people with recurrent hypogly cemia; i.e., patients with intensively treated diabetes or an insulinoma have symptoms at glucose levels lower than those that cause symptoms in healthy individuals. Clinical Manifestations Neuroglycopenic manifestations of hypoglycemia are the direct result of central nervous system glucose deprivation. These features include behavioral changes, confusion, fatigue, seizure, loss of consciousness, cardiac arrhythmias, and, if hypoglycemia is severe, death. Neurogenic (or autonomic) manifes tations of hypoglycemia result from the

perception of physiologic changes caused by the central nervous system–mediated sympa thoadrenal discharge that is triggered by hypoglycemia. They include adrenergic symptoms (mediated largely by norepinephrine released from sympathetic postganglionic neurons but perhaps also by epineph rine released from the adrenal medullae), such as palpitations, tremor, and anxiety, as well as cholinergic symptoms (mediated by acetylcholine released from sympathetic postganglionic neurons), such as sweating, hunger, and paresthesias. Clearly, these are nonspecific symptoms. Their attribution to hypoglycemia requires that the corresponding plasma glucose concentration be low and that the symptoms resolve after the glucose level is raised (as delineated by Whipple's triad). Common signs of hypoglycemia include diaphoresis and pallor. Heart rate and systolic blood pressure are typically increased but may not be raised in an individual who has experienced repeated, recent episodes of hypoglycemia. Neuroglycopenic manifestations are often observable. Transient focal neurologic deficits occur occasionally. Per manent neurologic deficits are rare. Etiology and Pathophysiology Hypoglycemia activates proin flammatory, procoagulant, and proatherothrombotic responses in type 1

diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and nondi abetic individuals. These responses increase platelet aggregation, reduce fibrinolytic balance (increase plasminogen activator inhibitor-1), and increase intravascular coagulation. Hypoglycemia also reduces protec tive nitric oxide–mediated arterial vasodilator mechanisms in healthy, T1DM, and T2DM individuals. ■ ■HYPOGLYCEMIA IN DIABETES Impact and Frequency Hypoglycemia is the limiting factor in the glycemic management of diabetes mellitus. First, it causes

ROLE IN PREVENTION OR CORRECTION OF HYPOGLYCEMIA (GLUCOSE COUNTERREGULATION) Primary glucose regulatory factor/first defense against hypoglycemia Third defense against hypoglycemia; critical when glucagon is deficient recurrent morbidity in most people with T1DM and in many with advanced T2DM, and it is sometimes fatal. Second, it precludes maintenance of euglycemia over a lifetime of diabetes and, thus, full realization of the well-established microvascular benefits of glycemic control. Third, it causes a vicious cycle of recurrent hypoglycemia by producing hypoglycemia-associated autonomic failure—i.e., the clinical syndromes of defective glucose counterregulation and of hypo glycemia unawareness. Hypoglycemia is a fact of life for people with T1DM if treated with insulin, sulfonylurea, or glinides. They suffer an average of two epi sodes of symptomatic hypoglycemia per week and at least one episode of severe, at least temporarily disabling hypoglycemia each year. An estimated 6–10% of people with T1DM die as a result of hypoglycemia. The incidence of hypoglycemia is lower in T2DM than in T1DM. How ever, its prevalence in insulin-requiring T2DM is surprisingly high. Recent studies have revealed a hypoglycemia prevalence approaching 70%. In fact, as patients with T2DM outnumber those with T1DM by 10- to 20-fold, the prevalence of hypoglycemia is now greater in T2DM. Hypoglycemia can occur at any hemoglobin A1c (HbA1c) level. Although severe hypoglycemia occurs twice as frequently at lower HbA1c levels in T1DM, it still occurs at HbA1c levels >8%. In insulinrequiring T2DM, severe hypoglycemia can occur at lower HbA1c values but also importantly at values of 8–10%. Severe hypoglycemia in T2DM carries an increased risk of severe cardiovascular and cerebrovascular morbidity and mortality for up to 1 year after the event. The risk of severe hypoglycemia and a subsequent cardiovascular adverse event is, in fact, relatively increased when trying to improve glucose control in some T2DM individuals with persistently raised HbA1c values. There fore, improvements in glycemic control in these individuals should be performed incrementally and carefully to avoid episodes of hypo glycemia. Insulin,

sulfonylureas, or glinides can cause hypoglycemia in T2DM. Metformin, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 inhibitors, and dipeptidyl peptidase IV (DPP-IV) inhibitors do not cause hypoglycemia. However, they increase the risk when combined with a sulfonylurea, glinide, or insulin. Notably, the frequency of hypoglycemia approaches that in T1DM as persons with T2DM develop absolute insulin deficiency and require more complex treatment with insulin. Conventional Risk Factors The conventional risk factors for hypoglycemia in diabetes are identified on the basis of relative or abso lute insulin excess. This occurs when (1) insulin (or insulin secreta gogue) doses are excessive, ill-timed, or of the wrong type; (2) the influx of exogenous glucose is reduced (e.g., during an overnight fast, periods of temporary fasting, or after missed meals or snacks); (3) insulinindependent glucose utilization is increased (e.g., during exercise); (4) sensitivity to insulin is increased (e.g., with improved glycemic control,

in the middle of the night, after exercise, or with increased fitness or weight loss); (5) endogenous glucose production is reduced (e.g., after alcohol ingestion); and (6) insulin clearance is reduced (e.g., in renal failure). However, these conventional risk factors alone explain a minority of episodes; other factors are typically involved. Hypoglycemia-Associated Autonomic Failure (HAAF) While marked insulin excess alone can cause hypoglycemia, iatrogenic hypo glycemia in diabetes (T1DM and/or T2DM) is typically the result of the interplay of relative or absolute therapeutic insulin excess and com promised physiologic and behavioral defenses against falling plasma glucose concentrations (Table 418-2; Fig. 418-2). Defective glucose counterregulation compromises physiologic defense (particularly dec rements in insulin and increments in glucagon and epinephrine), and hypoglycemia unawareness compromises behavioral defense (ingestion of carbohydrate). DEFECTIVE GLUCOSE COUNTERREGULATION In the setting of abso lute endogenous insulin deficiency, insulin levels do not decrease as plasma glucose levels fall; thus, the first defense against hypoglycemia is lost. After a few years of disease duration in T1DM, glucagon levels do not increase as plasma glucose levels fall; a second defense against hypoglycemia is lost. Reduced glucagon responses to hypoglycemia also occur in long-duration T2DM. However, pancreatic alpha cells that produce glucagon are present in the same number and size in T1DM as compared to age-matched nondiabetic individuals. Thus, the defect that restricts glucagon release during hypoglycemia in T1DM (and presumably in long-standing T2DM) appears to be a signaling defect, as glucagon responses to other physiologic stress in T1DM (e.g., exercise) are preserved. Finally, the increase in epinephrine lev els, the third critical defense against acute hypoglycemia, is typically attenuated. The glycemic threshold for the sympathoadrenal (adre nomedullary epinephrine and sympathetic neural norepinephrine) response is shifted to lower plasma glucose concentrations. That shift is typically the result of recent antecedent iatrogenic hypoglycemia. In Early T2DM (Relative β-cell failure) Advanced T2DM and T1DM (Absolute β-cell failure) Marked absolute therapeutic hyperinsulinemia → Falling glucose levels Relative or mild-moderate absolute therapeutic hyperinsulinemia → Falling glucose levels β-cell failure → No ↓ insulin and no ↑ glucagon Isolated episodes of hypoglycemia Episodes of hypoglycemia Sleep Exercise Attenuated sympathoadrenal responses to hypoglycemia (HAAF) ↓ Adrenomedullary epinephrine responses ↓ Sympathetic neural responses Hypoglycemia unawareness Defective glucose counterregulation Recurrent hypoglycemia FIGURE 418-2 Hypoglycemia-associated autonomic failure (HAAF) in insulin-deficient diabetes. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. (Reprinted with permission from The American Diabetes Association. Copyright 2012 by the American Diabetes Association.)

the setting of absent decrements in insulin and of absent increments in glucagon, the attenuated increment in epinephrine causes the clinical syndrome of defective glucose counterregulation. Affected patients are at ≥25-fold greater risk of severe iatrogenic hypoglycemia during intensive glycemic therapy for their diabetes than are patients with nor mal epinephrine responses. This functional—and potentially revers ible—disorder is distinct from classic diabetic autonomic neuropathy, which also includes all of the above pathophysiologic defects, and is a structural and irreversible disorder.

HYPOGLYCEMIA UNAWARENESS The attenuated sympathoadrenal response (largely the reduced sympathetic neural response) to hypogly cemia causes the clinical syndrome of hypoglycemia unawareness—i.e., loss of the warning adrenergic and cholinergic symptoms that previ ously allowed the patient to recognize developing hypoglycemia and therefore to abort the episode by ingesting carbohydrates. Affected patients are at a sixfold increased risk of severe iatrogenic hypoglyce mia during intensive glycemic therapy of their diabetes. Hypoglycemia CHAPTER 418 HAAF IN DIABETES The concept of HAAF in diabetes posits that recent antecedent iatrogenic hypoglycemia (or sleep or prior exercise) causes both defective glucose counterregulation (by reducing the epi nephrine response to a given level of subsequent hypoglycemia in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathoadrenal response to a given level of subsequent hypoglycemia). These impaired responses, which can occur in individuals with either T1DM or T2DM, create a vicious cycle of recurrent iatrogenic hypoglycemia (Fig. 418-2). Hypoglycemia unawareness and, to some limited extent, the reduced epinephrine component of defective glucose counterregulation can be reversible by as little as 2–3 weeks of scrupulous avoidance of hypoglycemia in most affected patients. On the basis of this pathophysiology, additional risk factors for hypoglycemia in diabetes include (1) absolute insulin deficiency, indi cating that insulin levels will not decrease and glucagon levels will not increase as plasma glucose levels fall; (2) a history of severe hypoglycemia or of hypoglycemia unaware ness, implying recent antecedent hypoglycemia, as well as prior exercise or sleep, indicating that the sympathoadrenal response will be attenuated; (3) impaired renal function resulting in reduced clear ance of exogenous and endogenous insulin; (4) clas sical diabetic autonomic neuropathy; and (5) lower HbA1c or lower glycemic goals even at elevated HbA1c levels (8–10%), as they represent an increased prob ability of recent antecedent hypoglycemia. Hypoglycemia Risk Factor Reduction Several multicenter, randomized controlled trials investigat ing the potential benefits of tight glucose control in either inpatient or outpatient settings have reported a high prevalence of severe hypoglycemia. In the NICESUGAR study, attempts to control in-hospital plasma glucose values toward physiologic levels resulted in increased mortality risk. The ADVANCE and ACCORD studies and the Veterans Affairs Diabetes Trial (VADT) also found a significant incidence of severe hypoglycemia among T2DM patients. Severe hypoglycemia with accompanying serious cardio vascular morbidity and mortality also occurred in the standard (e.g., not receiving intensified treat ment) control group in all of the above studies and in another large study in prediabetic and T2DM individuals (ORIGIN). Thus, as stated above, severe hypoglycemia can and does occur at HbA1c values of 8–10% in both T1DM and T2DM. Somewhat sur prisingly, all three studies found little or no benefit of intensive glucose control to reduce macrovascular events in T2DM. In fact, the ACCORD study was ended early because of the increased mortality rate in the intensive glucose control arm. Whether iatrogenic

hypoglycemia was the cause of the increased mortality risk is not known. In light of these findings, some new recommendations and par adigms have been formulated. Whereas there is little debate regarding the need to reduce hyperglycemia in the hospital, the glycemic mainte nance goals in critical care settings have been modified to stay between 140 and 180 mg/dL. Similar glycemic targets are also recommended in non–critically ill patients by a number of expert societies, although some recommend even more strict glucose control down to 108 mg/dL. Accordingly, the benefits of insulin therapy and reduced hyperglycemia can be obtained while the prevalence of hypoglycemia is reduced.

Similarly, evidence exists that intensive glucose control can reduce the prevalence of microvascular disease in both T1DM and T2DM. These benefits need to be weighed against the increased prevalence of hypoglycemia. Certainly, the level of glucose control (i.e., the HbA1c value, symptoms of hyper- and hypoglycemia, and home glucose val ues) should be evaluated for each patient. Multicenter trials have dem onstrated that individuals with recently diagnosed T1DM or T2DM can have better glycemic control with less hypoglycemia. In addition, there is still long-term benefit in reducing HbA1c values from higher to lower, albeit still above recommended levels. Perhaps a reasonable therapeutic goal is the lowest HbA1c level that does not cause severe hypoglycemia and that preserves awareness of hypoglycemia. PART 12 Endocrinology and Metabolism Recent studies have demonstrated the benefit of second-generation basal and prandial analogue insulins in reducing the risk of both nonsevere and severe hypoglycemia. The reduction of hypoglycemia occurred during both the day and night and was observed in T1DM and T2DM individuals. Addition of longer acting GLP-1 and dual GLP-1/gastric inhibitory polypeptide (GIP) receptor agonists to a basal insulin in the management of insulin-requiring T2DM has also resulted in lower hypoglycemic risk as compared to a basal insulin and a first-generation prandial insulin analogue. Pancreatic transplantation (both whole organ and islet cell) has been used in part as a treatment for severe hypoglycemia. Generally, rates of hypoglycemia are reduced after transplantation. This decrease appears to be due to increased physiologic insulin and glucagon responses during hypoglycemia. The use of continuous glucose monitors (CGMs), either alone or in combination with continuous subcutaneous infusion via a wearable pump, offers promise as a method of reducing hypoglycemia while improving HbA1c. Specifically, continuous glucose monitoring coupled with temporary discontinuation of subcutaneous insulin infusion when the monitor predicts a low glucose concentration is particularly promising. Studies investigating the use of CGM during inpatient care for both insulin-requiring pediatric and adult patients with diabetes are ongoing. Furthermore, progress utilizing a portable wearable closedloop automated “artificial pancreas” or sensor-augmented pump therapy incorporating continuous glucose modulation of either insulin alone or bi-hormonal delivery of both insulin and glucagon has been established. Additionally, stem cell–derived β cells also offer promise of novel therapeutic interventions to reduce hypoglycemia. Nonpharmacologic approaches of hypoglycemia risk reduction utilizing structured patient education have also been proven to be successful in T1DM and T2DM. Outpatient education consisting of adjustment of meal plans, exercise, and medications, combined with early recognition and treatment of hypoglycemia, have all been demonstrated to reduce hypoglycemic risk with even small improvements in HbA1c. Other interventions to stimulate counter regulatory responses, such as selective serotonin reuptake inhibitors, β-adrenergic receptor antagonists, opiate receptor antagonists, and fructose, remain experimental and have not been assessed in largescale clinical trials. Thus, intensive glycemic therapy (Chap. 416) needs to be applied along with the patient’s education and empowerment, frequent selfmonitoring of blood

glucose, flexible insulin (and other drug) regimens (including the use of insulin analogues, both short- and longer-acting), individualized glycemic goals, and ongoing professional guidance, sup port, and consideration of both the conventional risk factors and those indicative of compromised glucose counterregulation. Given a history of hypoglycemia unawareness, a 2- to 3-week period of scrupulous avoidance of hypoglycemia is indicated.

■ ■HYPOGLYCEMIA WITHOUT DIABETES There are many causes of hypoglycemia (Table 418-1). Because hypo glycemia is common in insulin- or insulin secretagogue–treated diabe tes, it is often reasonable to assume that a clinically suspicious episode is the result of hypoglycemia. On the other hand, because hypoglyce mia is rare in the absence of relevant drug-treated diabetes (pregnancy and during severe episodes of morning sickness), it is reasonable to conclude that a hypoglycemic disorder is present only in patients in whom Whipple's triad can be demonstrated. Particularly when patients are ill or medicated, the initial diag nostic focus should be on the possibility of drug involvement and then on critical illnesses, hormone deficiency, or non–islet cell tumor hypoglycemia. In the absence of any of these etiologic factors and in a seemingly well individual, the focus should shift to possible endog enous hyperinsulinism or accidental, surreptitious, or even malicious hypoglycemia. Drugs Insulin and insulin secretagogues suppress glucose produc tion and stimulate glucose utilization. Ethanol blocks gluconeogenesis but not glycogenolysis. Thus, alcohol-induced hypoglycemia typically occurs after a several-day ethanol binge during which the person eats little food, with consequent glycogen depletion. Ethanol is usually measurable in blood at the time of presentation, but its levels correlate poorly with plasma glucose concentrations. Because gluconeogenesis becomes the predominant route of glucose production during pro longed hypoglycemia, alcohol can contribute to the progression of hypoglycemia in patients with insulin-treated diabetes. Many other drugs have been associated with hypoglycemia. These include commonly used drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, β-adrenergic recep tor antagonists, quinolone antibiotics, indomethacin, quinine, and sulfonamides. Critical Illness Among hospitalized patients, serious illnesses such as renal, hepatic, or cardiac failure; sepsis; and inanition are second only to drugs as causes of hypoglycemia. Rapid and extensive hepatic destruction (e.g., toxic hepatitis) causes fasting hypoglycemia because the liver is the major site of endogenous glucose production. The mechanism of hypoglycemia in patients with cardiac failure is unknown. Hepatic congestion and hypoxia may be involved. Although the kidneys are a source of glucose produc tion, hypoglycemia in patients with renal failure is also caused by the reduced clearance of insulin (thereby inappropriately increasing insu lin relative to the prevailing glucose levels) and the reduced mobiliza tion of gluconeogenic precursors in renal failure. Sepsis is a relatively common cause of hypoglycemia. Increased glucose utilization is induced by cytokine production in macrophagerich tissues such as the liver, spleen, and lung. Hypoglycemia develops if glucose production fails to keep pace. Cytokine-induced inhibition of gluconeogenesis in the setting of nutritional glycogen depletion, in combination with hepatic and renal hypoperfusion, may also contrib ute to hypoglycemia. Hypoglycemia can be seen with starvation. Due to brain conversion and utilization of alternative substrates, such as lactate, pyruvate, and ketone bodies, there is only a modest counterregulatory neuroendo crine and autonomic nervous system response. During periods of pro longed starvation (fasting), plasma glucose levels are lower in women as compared to men, perhaps because of loss of whole-body fat stores and subsequent depletion of gluconeogenic precursors (e.g., amino acids), necessitating increased glucose utilization. Hormone Deficiencies Neither cortisol nor growth hormone is critical to the prevention of hypoglycemia, at

least in adults. Nonethe less, hypoglycemia can occur with prolonged fasting in patients with primary adrenocortical failure (Addison's disease) or hypopituitarism. Anorexia and weight loss are typical features of chronic cortisol defi ciency and likely result in glycogen depletion. Cortisol deficiency is associated with impaired gluconeogenesis and low levels of gluco neogenic precursors; these associations suggest that substrate-limited gluconeogenesis, in the setting of glycogen depletion, is the cause of

hypoglycemia. Growth hormone deficiency can cause hypoglycemia in young children. In addition to extended fasting, high rates of glucose utilization (e.g., during exercise or in pregnancy) or low rates of glucose production (e.g., after alcohol ingestion) can precipitate hypoglycemia in adults with previously unrecognized hypopituitarism. Hypoglycemia is not a feature of the epinephrine-deficient state that results from bilateral adrenalectomy when glucocorticoid replacement is adequate, nor does it occur during pharmacologic adrenergic block ade when other glucoregulatory systems are intact. Combined deficien cies of glucagon and epinephrine play a key role in the pathogenesis of iatrogenic hypoglycemia in people with insulin-deficient diabetes, as discussed earlier. Otherwise, deficiencies of these hormones are not usually considered in the differential diagnosis of a hypoglycemic disorder. Non–β-Cell Tumors Fasting hypoglycemia, often termed non–islet cell tumor hypoglycemia, occurs occasionally in patients with large mesenchymal or epithelial tumors (e.g., hepatomas, adrenocortical carcinomas, carcinoids). The glucose kinetic patterns resemble those of hyperinsulinism (see next), but insulin secretion is suppressed appro priately during hypoglycemia. In most instances, hypoglycemia is due to overproduction of an incompletely processed form of insulin-like growth factor II ("big IGF-II") that does not complex normally with circulating binding proteins and thus more readily gains access to tar get tissues. The tumors are usually apparent clinically, plasma ratios of IGF-II to IGF-I are high, and free IGF-II levels (and levels of pro-IGF-II [1–21]) are elevated. Curative surgery is seldom possible, but reduction of tumor bulk may ameliorate hypoglycemia. Therapy with a gluco corticoid, growth hormone, or both has also been reported to alleviate hypoglycemia. Hypoglycemia attributed to ectopic IGF-I production has been reported but is rare. Endogenous Hyperinsulinism Hypoglycemia due to endog enous hyperinsulinism can be caused by (1) a primary β-cell disorder— typically a β-cell tumor (insulinoma), sometimes multiple insulinomas, or a functional β-cell disorder with β-cell hypertrophy or hyperplasia; (2) an antibody to insulin or to the insulin receptor; (3) a β-cell secre tagogue such as a sulfonylurea; or perhaps (4) ectopic insulin secretion, among other very rare mechanisms. None of these causes are common. The fundamental pathophysiologic feature of endogenous hyperin sulinism caused by a primary β-cell disorder or an insulin secretagogue is the failure of insulin secretion to fall to very low levels during hypo glycemia. This feature is assessed by measurement of plasma insulin, C-peptide (the connecting peptide that is cleaved from proinsulin to produce insulin), proinsulin, and glucose concentrations during hypo glycemia. Insulin, C-peptide, and proinsulin levels need not be high rela tive to normal, euglycemic values; rather, they are inappropriately high in the setting of a low plasma glucose concentration. Critical diagnostic findings are a plasma insulin concentration ≥3 μU/mL (≥18 pmol/L), a plasma C-peptide concentration ≥0.6 ng/mL (≥0.2 nmol/L), and a plasma proinsulin concentration ≥5.0 pmol/L when the plasma glucose concentration is <55 mg/dL (<3.0 mmol/L) with symptoms of hypogly cemia. A low plasma β-hydroxybutyrate concentration (≤2.7 mmol/L) and an increment in plasma glucose level of >25 mg/dL (>1.4 mmol/L) after IV administration of glucagon (1.0 mg) indicate increased insulin (or IGF) actions. The diagnostic strategy is (1) to measure plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate concentrations and to screen for circulating oral

hypoglycemic agents during an episode of hypoglycemia and (2) to assess symptoms during the episode and seek their resolution following correction of hypoglycemia by glucose (either oral or parenteral) or by IV injection of glucagon (i.e., to docu ment Whipple's triad). This is straightforward if the patient is hypo glycemic when seen. Since endogenous hyperinsulinemic disorders usually, but not invariably, cause fasting hypoglycemia, a diagnostic episode may develop after a relatively short outpatient fast. Serial sampling during an inpatient diagnostic fast of up to 72 h or after a mixed meal is more problematic. An alternative is to give patients a detailed list of the required measurements and ask them to present to an ambulatory care center or emergency room, with the list, during a

symptomatic episode. Obviously, a normal plasma glucose concentra tion during a symptomatic episode indicates that the symptoms are not the result of hypoglycemia.

An insulinoma—an insulin-secreting pancreatic islet β-cell tumor— is the prototypical cause of endogenous hyperinsulinism and therefore should be sought in patients with a compatible clinical syndrome. However, insulinoma is not the only cause of endogenous hyperin sulinism. Some patients with fasting endogenous hyperinsulinemic hypoglycemia have diffuse islet involvement with β-cell hypertrophy and sometimes hyperplasia. This pattern is commonly referred to as nesidioblastosis, although β cells budding from ducts are not invariably found. Other patients have a similar islet pattern but with postpran dial hypoglycemia, a disorder termed noninsulinoma pancreatogenous hypoglycemia. Post–gastric bypass postprandial hypoglycemia, which most often follows Roux-en-Y gastric bypass, is also characterized by diffuse islet involvement and endogenous hyperinsulinism. Multiple pathophysiologic mechanisms have been suggested including exag gerated GLP-1 responses to meals resulting in hyperinsulinemia, hypoglucagonemia, and hypoglycemia. However, other mechanisms may be responsible for the relative hyperinsulinemia, such as reduced insulin clearance and reduced glucagon responses to hypoglycemia. The relevant pathogenesis has not been clearly established. However, if medical treatment with agents such as an α-glucosidase inhibitor, diazoxide, or octreotide fails, partial pancreatectomy may be required. Autoimmune hypoglycemias include those caused by an antibody to insulin that binds postmeal insulin and then gradually disassociates, with consequent late postprandial hypoglycemia. Alternatively, an insulin receptor antibody can function as an agonist. The presence of an insulin secretagogue, such as a sulfonylurea or a glinide, results in a clinical and biochemical pattern similar to that of an insulinoma but can be distinguished by the presence of the circulating secretagogue. Finally, there are reports of very rare phenomena such as ectopic insulin secretion, a gain-of-function insulin receptor mutation, and exercise-induced hyperinsulinemia. Hypoglycemia CHAPTER 418 Insulinomas are uncommon, with an estimated yearly incidence of 1 in 250,000. Because >90% of insulinomas are benign, they are a treat able cause of potentially fatal hypoglycemia. The median age at presen tation is 50 years in sporadic cases, but the tumor usually presents in the third decade when it is a component of multiple endocrine neopla sia type 1 (Chap. 400). More than 99% of insulinomas are within the substance of the pancreas, and the tumors are usually small (<2.0 cm in diameter in 90% of cases). Therefore, they come to clinical attention because of hypoglycemia rather than mass effects. Computed tomog raphy or magnetic resonance imaging detects ~70–80% of insulinomas. These methods detect metastases in the roughly 10% of patients with a malignant insulinoma. Transabdominal ultrasound often identifies insulinomas, and endoscopic ultrasound has a sensitivity of ~90%. Somatostatin receptor scintigraphy is thought to detect insulinomas in about half of patients.

Selective pancreatic arterial calcium injec tions, with the endpoint of a sharp increase in hepatic venous insulin levels, regionalize insulinomas with high sensitivity, but this invasive procedure is seldom necessary except to confirm endogenous hyperin sulinism in the diffuse islet disorders. Intraoperative pancreatic ultra sonography almost invariably localizes insulinomas that are not readily palpable by the surgeon. Surgical resection of a solitary insulinoma is generally curative. Diazoxide, which inhibits insulin secretion, or the somatostatin analogue octreotide can be used to treat hypoglycemia in patients with unresectable tumors; everolimus, an mTOR (mammalian target of rapamycin) inhibitor, has also been successful in combination with the above approaches. ■ ■ACCIDENTAL, SURREPTITIOUS, OR MALICIOUS HYPOGLYCEMIA Accidental ingestion of an insulin secretagogue (e.g., as the result of a pharmacy or other medical error) or even accidental administration of insulin can occur. Factitious hypoglycemia, caused by surreptitious or even malicious administration of insulin or an insulin secretagogue, shares many clinical and laboratory features with insulinoma. It is most common among health care workers, patients with diabetes or

their relatives, and people with a history of other factitious illnesses. However, it should be considered in all patients being evaluated for hypoglycemia of obscure cause. Ingestion of an insulin secretagogue causes hypoglycemia with increased C-peptide levels, whereas exoge nous insulin causes hypoglycemia with low C-peptide levels, reflecting suppression of insulin secretion.

Analytical error in the measurement of plasma glucose concentra tions is rare. On the other hand, hand-held and continuous glucose monitors used to guide treatment of diabetes are not quantitative instruments, particularly at low glucose levels, and should not be used for the definitive diagnosis of hypoglycemia. Even with a quantitative method, low measured glucose concentrations can be artifactual—e.g., the result of continued glucose metabolism by the formed elements of the blood ex vivo, particularly in the presence of leukocytosis, eryth rocytosis, or thrombocytosis or with delayed separation of the serum from the formed elements (pseudohypoglycemia). PART 12 Endocrinology and Metabolism ■ ■INBORN ERRORS OF METABOLISM

CAUSING HYPOGLYCEMIA Nondiabetic hypoglycemia also results from inborn errors of metabo lism. Such hypoglycemia most commonly occurs in infancy but can also occur in adulthood. Cases in adults can be classified into those resulting in fasting hypoglycemia, postprandial hypoglycemia, and exercise-induced hypoglycemia. Fasting Hypoglycemia Although rare, disorders of glycogenolysis can result in fasting hypoglycemia. These disorders include glycogen storage disease (GSD) of types 0, I, III, and IV and Fanconi-Bickel syndrome (Chap. 430). Patients with GSD types I and III characteristi cally have high blood lactate levels before and after meals, respectively. Both groups have hypertriglyceridemia, but ketones are high in GSD type III. Defects in fatty acid oxidation also result in fasting hypogly cemia. These defects can include (1) defects in the carnitine cycle;

(2) fatty-acid β-oxidation disorders; (3) electron transfer disturbances; and (4) ketogenesis disorders. Finally, defects in gluconeogenesis (fructose-1,6-biphosphatase) have been reported to result in recurrent hypoglycemia and lactic acidosis. Postprandial Hypoglycemia Inborn errors of metabolism result ing in postprandial hypoglycemia are also rare. These errors include (1) glucokinase, SUR1, and Kir6.2 potassium channel mutations; (2) congenital disorders of glycosylation; and (3) inherited fructose intolerance. Exercise-Induced Hypoglycemia Exercise-

induced hypogly cemia, by definition, follows exercise. It results in hyperinsulinemia caused by increased activity of monocarboxylate transporter 1 in

β cells. APPROACH TO THE PATIENT Hypoglycemia In addition to the recognition and documentation of hypoglycemia as well as its treatment (often on an urgent basis), diagnosis of the hypoglycemic mechanism is critical for the selection of therapy that prevents, or at least minimizes, recurrent hypoglycemia. RECOGNITION AND DOCUMENTATION Hypoglycemia is suspected in patients with typical symptoms; in the presence of confusion, an altered level of consciousness, or a seizure; or in a clinical setting in which hypoglycemia is known to occur. Blood should be drawn, whenever possible, before the administration of glucose to allow documentation of a low plasma glucose concentration. Convincing documentation of hypoglyce mia requires the fulfillment of Whipple's triad. Thus, the ideal time to measure the plasma glucose level is during a symptomatic episode. A normal glucose level excludes hypoglycemia as the cause of the symptoms. A low glucose level confirms that hypoglycemia is the cause of the symptoms, provided the latter resolve after the glucose level is raised. When the cause of the hypoglycemic

episode is obscure, additional measurements—made while the glucose level is low and before treatment—should include plasma insulin, C-peptide, proinsulin, and β-hydroxybutyrate levels; also critical are screening for circulating oral hypoglycemic agents and assessment of symptoms before and after the plasma glucose con centration is raised. When the history suggests prior hypoglycemia and no poten tial mechanism is apparent, the diagnostic strategy is to evaluate the patient as just described and assess for Whipple's triad during and after an episode of hypoglycemia. On the other hand, while it cannot be ignored, a distinctly low plasma glucose concentration measured in a patient without corresponding symptoms raises the possibility of an artifact (pseudohypoglycemia). DIAGNOSIS OF THE HYPOGLYCEMIC MECHANISM In a patient with documented hypoglycemia, a plausible hypogly cemic mechanism can often be deduced from the history, physical examination, and available laboratory data (Table 418-1). Drugs, particularly alcohol or agents used to treat diabetes, should be the first consideration—even in the absence of known use of a relevant drug—given the possibility of surreptitious, accidental, or mali cious drug administration. Other considerations include evidence of a relevant critical illness, hormone deficiencies (less commonly), and a non-β-cell tumor that can be pursued diagnostically (rarely). Absent one of these mechanisms in an otherwise seemingly well individual, the care provider should consider endogenous hyper insulinism and proceed with measurements and assessment of symptoms during spontaneous hypoglycemia or under conditions that might elicit hypoglycemia. URGENT TREATMENT If the patient is able and willing, oral treatment with glucose tab lets or glucose-containing fluids, candy, or food is appropriate. A reasonable initial dose is 15–20 g of glucose. If the patient is unable or unwilling (because of neuroglycopenia) to take carbohydrates orally, parenteral therapy is necessary. IV administration of glucose (25 g) should be followed by a glucose infusion guided by serial plasma glucose measurements. If IV therapy is not practical, SC or IM glucagon (1.0 mg in adults) can be used, particularly in patients with T1DM. Because it acts by stimulating glycogenolysis, glucagon is ineffective in glycogen-depleted individuals (e.g., those with alcohol-induced hypoglycemia). Glucagon also stimulates insulin secretion and is therefore less useful in T2DM. The somatostatin analogue octreotide can be used to suppress insulin secretion in sulfonylurea-induced hypoglycemia. These treatments raise plasma glucose concentrations only transiently, and patients should there fore be urged to eat as soon as is practical to replete glycogen stores. PREVENTION OF RECURRENT HYPOGLYCEMIA Prevention of recurrent hypoglycemia requires an understand ing of the hypoglycemic mechanism. Offending

drugs should be discontinued or their doses reduced. Hypoglycemia caused by a sulfonylurea can persist for hours or even days. Underlying critical illnesses can often be treated. Cortisol and growth hormone can be replaced if levels are deficient. Surgical, radiotherapeutic, or chemotherapeutic reduction of a non–islet cell tumor can alleviate hypoglycemia even if the tumor cannot be cured; glucocorticoid or growth hormone administration also may reduce hypoglycemic episodes in such patients. Surgical resection of an insulinoma is curative; medical therapy with diazoxide or octreotide can be used if complete resection is not possible and in patients with a nontu mor β-cell disorder. Partial pancreatectomy may be necessary in the latter patients. The treatment of autoimmune hypoglycemia (e.g., with glucocorticoid or immunosuppressive drugs) is problematic, but these disorders are sometimes self-limited. Failing these treat ments, frequent feedings and avoidance of fasting may be required. Administration of uncooked cornstarch at bedtime or even an overnight intragastric infusion of glucose may be necessary for some patients.

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