of hypoglycemia. The incidence of hypoglycemia is lower in T2DM than in T1DM. However, its prevalence in insulin-requiring T2DM is surprisingly high. Recent studies investigating insulin-pump or multiple-injection therapies have revealed a hypoglycemia prevalence approaching 70%. In fact, as patients with T2DM outnumber those with T1DM by ten- to twentyfold, the prevalence of hypoglycemia is now greater in T2DM. Insulin, a sulfonylurea, or a glinide can cause hypoglycemia in T2DM. Metformin, thiazolidinediones, α-glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase IV (DPP-IV) inhibitors should not cause hypoglycemia. However, they increase the risk when combined with one of the sulfonylureas or glinides, or with 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 the premise that relative or absolute insulin excess is the sole determinant of risk. Relative or absolute insulin excess occurs when (1) insulin (or insulin secretagogue) doses are excessive, ill-timed, or of the wrong type; (2) the influx of exogenous glucose is reduced (e.g., during an overnight fast or after missed meals or snacks); (3) insulin-independent 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, late 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 hypoglycemia in diabetes is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiologic and behavioral defenses against falling plasma glucose concentrations (Table 420-2; Fig. 420-2). Defective glucose counterregulation compromises physiologic defense (particularly decrements in insulin and increments in glucagon and epinephrine), and hypoglycemia unawareness compromises behavioral defense (ingestion of carbohydrate).

DEFECTIVE GLUCOSE COUNTERREGULATION In the setting of absolute endogenous insulin deficiency, insulin levels do not decrease as plasma glucose levels fall; the first defense against hypoglycemia is lost. Furthermore, probably because the decrement in intraislet insulin is normally a signal to stimulate glucagon secretion, glucagon levels do not increase as plasma glucose levels fall further; a second defense against hypoglycemia is lost. Finally, the increase in epinephrine levels, a third defense against hypoglycemia, in response to a given level of hypoglycemia is typically attenuated. The glycemic threshold for the sympathoadrenal (adrenomedullary 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 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 aggressive glycemic therapy for their diabetes than are patients with normal epinephrine responses. This functional—and potentially reversible—disorder is distinct from classic diabetic autonomic neuropathy—a structural and irreversible disorder.

HYPOGLYCEMIA UNAWARENESS The attenuated sympathoadrenal response (largely the reduced sympathetic neural response) to hypoglycemia causes the clinical syndrome of *hypoglycemia unawareness*—i.e., loss of the warning adrenergic and cholinergic symptoms that previously 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 hypoglycemia during aggressive glycemic therapy of their diabetes.

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 epinephrine 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 create a vicious cycle of recurrent iatrogenic hypoglycemia (Fig. 420-2). Hypoglycemia unawareness and, to some extent, the reduced epinephrine component of defective glucose counterregulation are 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, indicating 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 unawareness, implying recent antecedent hypoglycemia, as well as prior exercise or sleep, indicating that the sympathoadrenal response will be attenuated; and (3) lower hemoglobin A_{1c} (HbA_{1c}) levels or lower glycemic goals that, all other factors being equal, increase the probability of recent antecedent hypoglycemia.

Hypoglycemia Risk Factor Reduction Several recent multicenter, randomized, controlled trials investigating the potential benefits of tight

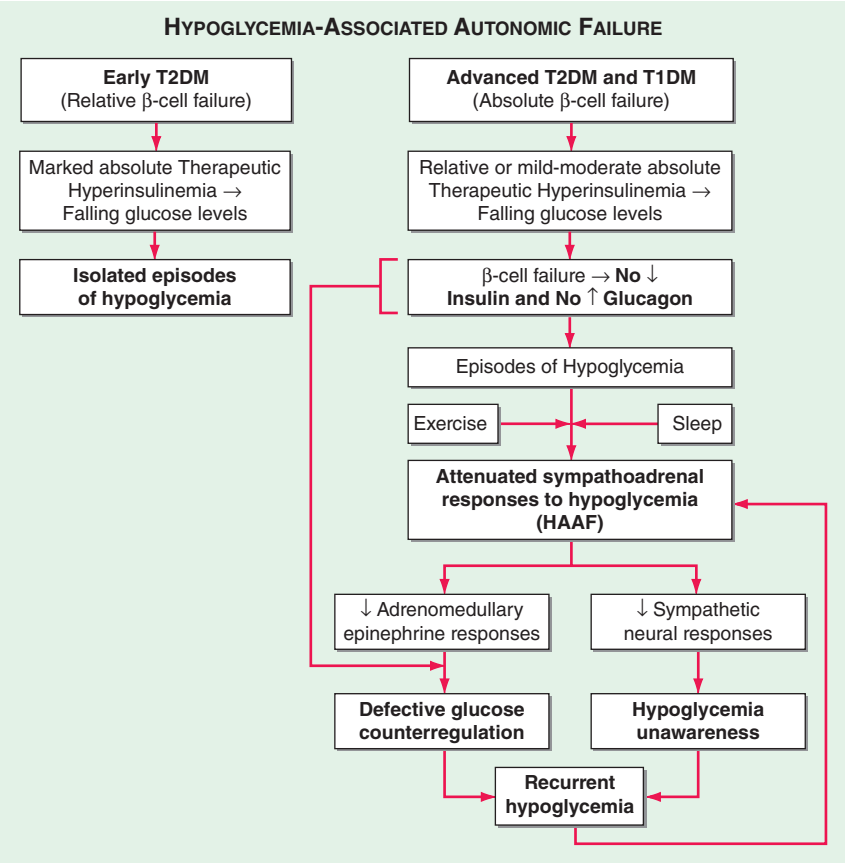

FIGURE 420-2 Hypoglycemia-associated autonomic failure (HAAF) in insulin-deficient diabetes. T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. *(Modified from PE Cryer: Hypoglycemia in Diabetes. Pathophysiology, Prevalence, and Prevention, 2nd ed. © American Diabetes Association, 2012.)*