Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline

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Objective: The aim is to provide guidelines for the evaluation and management of adults with hypoglycemic disorders, including those with diabetes mellitus.

Evidence: Using the recommendations of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system, the quality of evidence is graded very low (⊕◯◯◯), low (⊕⊕◯◯), moderate (⊕⊕⊕◯), or high (⊕⊕⊕⊕).

Conclusions: We recommend evaluation and management of hypoglycemia only in patients in whom Whipple's triad—symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after the plasma glucose concentration is raised—is documented. In patients with hypoglycemia without diabetes mellitus, we recommend the following strategy. First, pursue clinical clues to potential hypoglycemic etiologies—drugs, critical illnesses, hormone deficiencies, nonislet cell tumors. In the absence of these causes, the differential diagnosis narrows to accidental, surreptitious, or even malicious hypoglycemia or endogenous hyperinsulinism. In patients suspected of having endogenous hyperinsulinism, measure plasma glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and circulating oral hypoglycemic agents during an episode of hypoglycemia and measure insulin antibodies. Insulin or insulin secretagogue treatment of diabetes mellitus is the most common cause of hypoglycemia. We recommend the practice of hypoglycemia risk factor reduction—addressing the issue of hypoglycemia, applying the principles of intensive glycemic therapy, and considering both the conventional risk factors and those indicative of compromised defenses against falling plasma glucose concentrations—in persons with diabetes. **(*J Clin Endocrinol Metab* 94: 709–728, 2009)**

Summary of Recommendations

1.0 Workup for a hypoglycemic disorder

1.1 We recommend evaluation and management of hypoglycemia only in patients in whom Whipple's triad—symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after the plasma glucose concentration is raised—is documented (1⊕⊕⊕⊕).

2.0 Evaluation and management of hypoglycemia in persons without diabetes mellitus

2.1 Compared with a much less thorough workup, we recommend the following strategy in patients with hypoglycemia without diabetes mellitus (1⊕⊕⊕◯):

- Review the history, physical findings, and all available laboratory data seeking clues to specific disorders— drugs,

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Abbreviations: CSII, Continuous sc insulin infusion; HAAF, hypoglycemia-associated autonomic failure; HbA_{1C}, hemoglobin A_{1C}; MDI, multiple daily insulin injection; MEN-1, multiple endocrine neoplasia, type 1; MRI, magnetic resonance imaging; NIPHS, noninsulinoma pancreatogenous hypoglycemia syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

critical illnesses, hormone deficiencies, nonislet cell tumors.

- When the cause of the hypoglycemic disorder is not evident, *i.e.* in a seemingly well individual, measure plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate concentrations and screen for oral hypoglycemic agents, during an episode of spontaneous hypoglycemia, and observe the plasma glucose response to iv injection of 1.0 mg glucagon. These steps will distinguish hypoglycemia caused by endogenous (or exogenous) insulin from that caused by other mechanisms. Also, measure insulin antibodies.
- When a spontaneous hypoglycemic episode cannot be observed, formally recreate the circumstances in which symptomatic hypoglycemia is likely to occur, *i.e.* during a fast of up to 72 h or after a mixed meal. The findings of symptoms, signs, or both with plasma concentrations of glucose less than 55 mg/dl (3.0 mmol/liter), insulin of at least 3.0 μU/ml (18 pmol/liter), C-peptide of at least 0.6 ng/ml (0.2 nmol/liter), and proinsulin of at least 5.0 pmol/liter document endogenous hyperinsulinism; β-hydroxybutyrate levels of 2.7 mmol/liter or less and an increase in plasma glucose of at least 25 mg/dl (1.4 mmol/liter) after iv glucagon indicate mediation of the hypoglycemia by insulin (or by an IGF).
- In a patient with documented fasting or postprandial endogenous hyperinsulinemic hypoglycemia, negative screening for oral hypoglycemic agents, and no circulating insulin antibodies, conduct procedures for localizing an insulinoma. These may include computed tomography or magnetic resonance imaging (MRI), transabdominal and endoscopic ultrasonography, and, if necessary, selective pancreatic arterial calcium injections with measurements of hepatic venous insulin levels.
- Tailor treatment to the specific hypoglycemic disorder, taking into account the burden of hypoglycemia on patient well-being and patient preferences.

3.0 Evaluation and management of hypoglycemia in persons with diabetes mellitus

3.1 We suggest that persons with diabetes become concerned about the possibility of developing hypoglycemia when the self-monitored blood glucose concentration is falling rapidly or is no greater than 70 mg/dl (3.9 mmol/liter) (2⊕◯◯◯).

3.2 Given the established long-term microvascular benefits of glycemic control, we recommend that the therapeutic glycemic goal be the lowest mean glycemia [*e.g.* hemoglobin A_{1c} (HbA_{1C})] that can be accomplished safely in a given patient at a given point in the progression of that individual patient's diabetes (1⊕⊕⊕⊕).

3.3 We recommend that the prevention of hypoglycemia in diabetes involve addressing the issue in each patient contact and, if hypoglycemia is a problem, making adjustments in the regimen based on review and application of the principles of intensive glycemic therapy— diabetes self-management (supported by education and empowerment), frequent self-monitoring of blood glucose, flexible and appropriate insulin or insulin secretagogue regimens, individualized glycemic goals, and ongoing professional guidance and support—and consideration of each of the known risk factors for hypoglycemia (1⊕⊕⊕◯).

3.4 We recommend that both the conventional risk factors and those indicative of compromised defenses against hypoglycemia be considered in a patient with recurrent treatment-induced hypoglycemia (1⊕⊕⊕⊕). The conventional risk factors are excessive or ill-timed dosing of, or wrong type of, insulin or insulin secretagogue and conditions under which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization is increased, sensitivity to insulin is increased, or insulin clearance is decreased. Compromised defenses against hypoglycemia are indicated by the degree of endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise or sleep, and lower glycemic goals *per se*.

3.5 With a history of hypoglycemia unawareness (*i.e.* recurrent hypoglycemia without symptoms), we recommend a 2- to 3-wk period of scrupulous avoidance of hypoglycemia, with the anticipation that awareness of hypoglycemia will return in many patients (1⊕⊕◯◯).

3.6 Unless the cause is easily remediable, we recommend that an episode of severe hypoglycemia should lead to a fundamental review of the treatment regimen and the glycemic goals (1⊕⊕⊕⊕).

3.7 We recommend that urgent treatment of hypoglycemia should be accomplished by ingestion of carbohydrates if that is feasible, or by parenteral glucagon or glucose if it is not feasible (1⊕⊕⊕⊕).

Method of Development of Evidence-Based Recommendations

The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation system (1) with guidance from the methodologist (V.M.M.). A detailed description of this grading scheme has been published (2). In brief, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. The Task Force has confidence that patients who receive care according to the recommendations will derive, on average, more good than harm. Suggestions require more careful consideration of the patient's circumstances, values, and preferences. Cross-filled circles (⊕) indicate the quality of the evidence: ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The quality of the evidence indicates the panel's confidence that the estimates of risks and benefits associated with the recommended course of action compared with an alternative course of action are correct and unlikely to change importantly with new research.

Linked to each recommendation is a description of the *Evidence*, the *Values* that panelists considered in making the recommendation (when making these explicit was necessary), and *Remarks*, a section in which panelists offer technical suggestions for testing conditions. The latter come from the unsystematic observations of the panelists and should, therefore, be considered suggestions.

1.0 Workup for a Hypoglycemic Disorder

Recommendation

1.1 We recommend evaluation and management of hypoglycemia only in patients in whom Whipple's triad—symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after the plasma glucose concentration is raised—is documented (1⊕⊕⊕⊕).

1.1 Evidence

Clinical hypoglycemia is a plasma (or serum) glucose concentration low enough to cause symptoms and/or signs, including impairment of brain function. The clinical manifestations of hypoglycemia are nonspecific, it is not possible to state a single plasma glucose concentration that categorically defines hypoglycemia, and a low measured plasma glucose concentration can be artifactual. Therefore, hypoglycemia is confirmed by documentation of Whipple's triad (3): symptoms, signs, or both consistent with hypoglycemia, a low plasma glucose concentration, and resolution of those symptoms or signs after the plasma glucose concentration is raised. In the absence of Whipple's triad, the patient may be exposed to unnecessary evaluation, costs, and potential harms, without expectation of benefit. This very large potentially beneficial effect of documenting Whipple's triad upgrades the evidence (based on consistent clinical observations), thus supporting a rating of high quality. (A rare exception would be a patient who is physically unable to communicate symptoms.)

Symptoms of hypoglycemia are categorized as neuroglycopenic (the result of brain glucose deprivation *per se*) and neurogenic or autonomic (largely the result of the perception of physiological changes caused by the sympathoadrenal discharge triggered by hypoglycemia) (4). Awareness of hypoglycemia is mainly the result of the perception of neurogenic symptoms (4), which are largely sympathetic neural, rather than adrenomedullary, in origin (5). Some neurogenic symptoms, such as palpitations, tremor, and arousal/anxiety, are adrenergic whereas others, such as sweating, hunger, and paresthesias, are cholinergic (4). Neuroglycopenic symptoms (4) range from behavioral changes, fatigue, and confusion to seizure and loss of consciousness, *i.e.* functional brain failure (6). Seemingly complete recovery after the glucose level is raised is the rule, although on rare occasions neurological recovery is delayed. Profound, prolonged hypoglycemia can cause brain death (6). Signs of hypoglycemia, such as diaphoresis and pallor, are often subtle, although neuroglycopenic manifestations are often observable.

In healthy individuals, symptoms of hypoglycemia develop at a mean plasma glucose concentration of approximately 55 mg/dl (3.0 mmol/liter) (7). However, the glycemic thresholds for this and other responses to hypoglycemia shift to lower plasma glucose concentrations in patients with recurrent hypoglycemia (7–10). Furthermore, whereas arteriovenous plasma glucose concentration differences are clinically negligible in the postabsorptive state, antecubital venous plasma glucose concentrations are as much as one third lower than arterial glucose concentrations (which are relevant to maintaining brain glucose metabolism) when insulin secretion is increased substantially, *e.g.* after a glucose load, causing glucose extraction across the forearm (11). Finally, because of the provision of alternative circulating fuels to the brain (specifically ketones), lower plasma glucose concentrations occur in healthy individuals, particularly in women and children, without symptoms or signs during extended fasting (7). For all of these reasons, it is not possible to state a single plasma glucose concentration that categorically defines hypoglycemia.

Plasma glucose concentrations used to document Whipple's triad, in the absence of insulin or insulin secretagogue treatment of diabetes, must be measured with a reliable laboratory method, not with self-monitoring of blood glucose. Although a distinctly low, reliably measured plasma glucose concentration obtained in the absence of recognized symptoms or signs should not be ignored, that finding raises the possibility of "pseudohypoglycemia"—an artifact of continued glucose metabolism by the formed elements of the blood after the sample is drawn. That may occur when the blood sample is collected in a tube that does not contain an inhibitor of glycolysis and separation of the plasma (or serum) from the formed elements is delayed, particularly in the setting of erythrocytosis, leukocytosis, or thrombocytosis (12).

Documentation of Whipple's triad establishes that a hypoglycemic disorder exists. Its etiology may be apparent (*e.g.* in a patient with insulin-treated diabetes) or a diagnostic challenge (*e.g.* in a seemingly well individual with an insulinoma). On the other hand, in a person who does not have diabetes mellitus an unequivocally normal plasma glucose concentration [*e.g.* >70 mg/dl (3.9 mmol/liter) (7)] during a symptomatic episode indicates that those symptoms are not the result of hypoglycemia.

1.1 Values

Hypoglycemia is rare in persons who do not have drug-treated diabetes mellitus (12–15). Furthermore, not requiring Whipple's triad to initiate a workup will very likely expose patients who do not have a specific pathology causing hypoglycemia to unnecessary evaluations, costs, and potential harms without expectation of benefit. Therefore, we believe it is important to document Whipple's triad before concluding that a hypoglycemic disorder exists. On the other hand, hypoglycemia is common in persons with insulin- or insulin secretagogue-treated diabetes mellitus (12, 16). Confirmation of Whipple's triad, *e.g.* with self-monitoring of blood glucose, during an episode of suspected hypoglycemia is advisable in such a patient. However, if that is not practical, it is reasonable to assume the episode is caused by hypoglycemia for therapeutic purposes because the probability of that assumption is high and the potential negative impact of an untreated episode is considerable.

2.0 Evaluation and Management of Hypoglycemia in Persons without Diabetes Mellitus

Background

Because of the effectiveness of the normal defenses against falling plasma glucose concentrations (7), hypoglycemia is an

uncommon clinical event (12–15) except in persons who use drugs that lower plasma glucose levels, particularly insulin or an insulin secretagogue, to treat diabetes mellitus (12, 16). Hypoglycemia is a fact of life for most persons with type 1 diabetes and many with type 2 diabetes. Although persons with diabetes are not spared the risk for the same hypoglycemic disorders as those without diabetes, the vast majority of their hypoglycemic episodes are the result of treatment of their diabetes. Furthermore, the pathophysiology of hypoglycemia in diabetes is distinct, and the diagnostic and management approaches are different from those in individuals without diabetes (12, 16). Therefore, we address hypoglycemia in persons without diabetes and in those with diabetes separately.

Physiology and pathophysiology

Glucose is an obligate metabolic fuel for the brain under physiological conditions (6, 7). Because the brain cannot synthesize glucose, use physiological circulating concentrations of alternative fuels effectively, or store more than a few minutes' supply as glycogen, maintenance of brain function, and ultimately survival, requires a virtually continuous supply of glucose from the circulation. That, in turn, requires maintenance of the plasma glucose level within the physiological range because blood-to-brain glucose transport is a direct function of the arterial plasma glucose concentration. Redundant glucose counterregulatory mechanisms normally effectively prevent or rapidly correct hypoglycemia (7). The critical physiological defenses include: 1) a decrease in insulin secretion as glucose levels decline within the physiological range; 2) an increase in glucagon secretion; or, in its absence, 3) an increase in epinephrine secretion, both occurring as glucose levels decline just below the physiological range. Increased cortisol and GH secretion are involved in defense against prolonged hypoglycemia. If these defenses fail to abort the episode, plasma glucose levels will continue to fall. Symptoms, which prompt the behavioral defense of food ingestion, normally develop at a mean plasma glucose concentration of approximately 55 mg/dl (3.0 mmol/liter). At that and lower glucose levels, insulin secretion is suppressed virtually completely (7, 17); plasma insulin levels are below 3 μU/ml (18 pmol/liter), C-peptide levels are below 0.6 ng/ml (0.2 nmol/liter), and proinsulin levels are below 5.0 pmol/liter (14).

Because external losses are normally negligible, hypoglycemia develops when the sum of glucose utilization from the circulation (largely by the brain but also by obligatory glycolytic tissues, such as the renal medullae and erythrocytes, and insulin-sensitive tissues, such as muscle) exceeds the sum of glucose delivery into the circulation (from ingested carbohydrates and hepatic and renal glucose production) (12–15). Because of the capacity to increase endogenous glucose production substantially, hypoglycemia is typically the result of absolutely low rates of glucose production or rates of glucose production that are low relative to high rates of glucose utilization.

Recommendation

2.1 Compared with a much less thorough workup, we recommend the following strategy in patients with hypoglycemia without diabetes mellitus (1⊕⊕⊕◯):

- Review the history, physical findings, and all available laboratory data seeking clues to specific disorders— drugs, critical illnesses, hormone deficiencies, nonislet cell tumors.
- When the cause of the hypoglycemic disorder is not evident, *i.e.* in a seemingly well individual, measure plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate concentrations and screen for oral hypoglycemic agents, during an episode of spontaneous hypoglycemia, and observe the plasma glucose response to iv injection of 1.0 mg glucagon. These steps will distinguish hypoglycemia caused by endogenous (or exogenous) insulin from that caused by other mechanisms. Also, measure insulin antibodies.
- When a spontaneous hypoglycemic episode cannot be observed, formally recreate the circumstances in which symptomatic hypoglycemia is likely to occur, *i.e.* during a fast of up to 72 h or after a mixed meal. The findings of symptoms, signs, or both with plasma concentrations of glucose less than 55 mg/dl (3.0 mmol/liter), insulin of at least 3.0 μU/ml (18 pmol/liter), C-peptide of at least 0.6 ng/ml (0.2 nmol/liter), and proinsulin of at least 5.0 pmol/liter document endogenous hyperinsulinism; β-hydroxybutyrate levels of 2.7 mmol/liter or less and an increase in plasma glucose of at least 25 mg/dl (1.4 mmol/liter) after iv glucagon indicate mediation of the hypoglycemia by insulin (or by an IGF).
- In a patient with documented fasting or postprandial endogenous hyperinsulinemic hypoglycemia, negative screening for oral hypoglycemic agents, and no circulating insulin antibodies, conduct procedures for localizing an insulinoma. These may include computed tomography or MRI, transabdominal and endoscopic ultrasonography, and, if necessary, selective pancreatic arterial calcium injections with measurements of hepatic venous insulin levels.
- Tailor treatment to the specific hypoglycemic disorder, taking into account the burden of hypoglycemia on patient well-being and patient preferences.

2.1 Evidence

Because hypoglycemic disorders are rare in persons without diabetes, recommendations for their evaluation and management must rely largely on clinical experience. However, the implicit alternative approach to the recommendations we propose is a much less thorough clinical evaluation. Compared with this alternative, the large potential benefit of a thorough workup upgrades the quality of the evidence to moderate. Of note, however, much lower quality evidence supports the recommended strategy when compared with strategies with minor modifications or omissions.

General differential diagnosis

Causes of hypoglycemia are outlined in Table 1. Drugs are the most common cause of hypoglycemia (12, 18–21). In addition to insulin and insulin secretagogues, offending drugs include alcohol (12, 19, 20) among others, as detailed below. Hypoglycemia sometimes occurs during sepsis and in other critical illnesses including renal or hepatic failure, and rarely in cortisol deficiency (12). Hypoglycemia caused by nonislet cell tumors or endogenous hyperinsulinism is rare (12–15). It can also be accidental,

TABLE 1. Causes of hypoglycemia in adults

- Ill or medicated individual
  - 1. Drugs
    - Insulin or insulin secretagogue
    - Alcohol
    - Others (Table 2)
  - 2. Critical illnesses
    - Hepatic, renal, or cardiac failure
    - Sepsis (including malaria)
    - Inanition
  - 3. Hormone deficiency
    - Cortisol
    - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
  - 4. Nonislet cell tumor
- 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
    - Insulin secretagogue
    - Other
  - 6. Accidental, surreptitious, or malicious hypoglycemia

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

- Moderate quality of evidence (⊕⊕⊕◯)
  - Cibenzoline
  - Gatifloxacin
  - Pentamidine
  - Quinine
  - Indomethacin
  - Glucagon (during endoscopy)
- Low quality of evidence (⊕⊕◯◯)
  - Chloroquineoxaline sulfonamide
  - Artesunate/artemisin/artemether
  - IGF-I
  - Lithium
  - Propoxyphene/dextropropoxyphene
- Very low quality of evidence (⊕◯◯◯)
  - Drugs with >25 cases of hypoglycemia identified
    - Angiotensin converting enzyme inhibitors
    - Angiotensin receptor antagonists
    - β-Adrenergic receptor antagonists
    - Levofloxacin
    - Mifepristone
    - Disopyramide
    - Trimethoprim-sulfamethoxazole
    - Heparin
    - 6-Mercaptopurine
  - Drugs with <25 cases of hypoglycemia identified (see Ref. 24)

surreptitious, or even malicious (22). Hypoglycemia can occur as a result of hyperinsulinism in the absence of previous gastric surgery or after Roux-en-Y gastric bypass for obesity. It can also be caused by an antibody to insulin (12, 13, 15).

Classification of hypoglycemia

The traditional classification of hypoglycemia in persons without diabetes—postabsorptive (fasting) *vs.* postprandial (reactive) hypoglycemia—has been challenged (14). Persons with an insulinoma, who typically have postabsorptive hypoglycemia, may experience postprandial hypoglycemia, and post-gastric-bypass patients, who typically have postprandial hypoglycemia, may have symptoms when fasting. Indeed, some disorders, *e.g.* factitious hypoglycemia, are not readily classified as either postabsorptive or postprandial. Postprandial symptoms without Whipple's triad, previously called "reactive hypoglycemia," indicate a functional disorder in which symptoms are not due to hypoglycemia and for which an oral glucose tolerance test is not indicated (23). A more useful categorization for the clinician is to establish whether the patient is seemingly well or has the burden of a potentially relevant treatment or disease. With respect to the latter, it cannot be overemphasized that in any patient with hypoglycemia, mediation by a medication must be considered.

Drugs that can cause hypoglycemia

Many drugs in addition to insulin, insulin secretagogues, and alcohol have been reported to cause hypoglycemia (12–15, 18–21, 24). Many of these are listed in Table 2 (24).

Drugs, often in the setting of critical illnesses including renal failure, are the most common cause of hypoglycemia in hospitals (18). Again, insulin or insulin secretagogues are common offending drugs (18, 25), particularly when administered when enteral or parenteral nutrition is interrupted or when sensitivity to insulin is increased (*e.g.* after withdrawal of glucocorticoid therapy). Hypoglycemia is a sentinel event for many of the systems errors that compromise the safety of hospitalized patients (26). These include failure to reconcile admission orders with preadmission medications and diet, frequent transfers between hospital units, frequent travel of patients for radiological and surgical procedures and other diagnostic and therapeutic interventions, and inappropriate use of an insulin sliding scale.

Clinical evaluation

Persons with a hypoglycemic disorder present clinically with a history either of discrete spells compatible with hypoglycemia or of a serendipitously measured low plasma glucose concentration. Careful elicitation of the history of the spells, noting the specific symptoms, their timing and duration, and any aggravating and relieving factors, is essential for the formulation of a diagnostic course of action. Persons with only neurogenic symptoms (with no documented low glucose levels) are unlikely to have a hypoglycemic disorder. However, even one episode of neuroglycopenia warrants a diagnostic evaluation.

Initially, the history (including exposure to any medications), the physical examination, and a careful review of available laboratory data guide the evaluation. These will usually either provide clues to a cause of hypoglycemia or exclude hypoglycemia caused by acknowledged medications, critical illnesses, hormone deficiencies, or a nonislet cell tumor (Table 1). A test of adrenocortical function is reasonable, although adrenocortical failure is not commonly found as a cause of hypoglycemia in adults in the absence of other clinical clues. A seemingly low plasma cortisol concentration measured during spontaneous hypoglycemia is not sufficient evidence of adrenocortical insufficiency because of the effect of recurrent hypoglycemia to shift glycemic thresholds for cortisol secretion to lower plasma glucose concentrations (10). Although hypoglycemia in patients with nonislet cell tu-

mors is often the result of tumor overproduction of incompletely processed IGF-II (27), hypoglycemia attributed to overproduction of IGF-I has also been reported (28). Nonislet cell tumor hypoglycemia is usually, but not invariably, associated with large, clinically apparent mesenchymal tumors. The tumors typically secrete excessive amounts of pro-IGF-II. This form of IGF-II binds poorly to its binding proteins and therefore more freely penetrates tissue spaces. The total level of IGF-II may be normal, but the ratio of pro-IGF-II to IGF-II may be elevated; this can be demonstrated by chromatographic techniques, most easily and rapidly using thin layer chromatography (29). Because of suppressed GH secretion and the resulting low IGF-I levels, IGF-II to IGF-I ratios are elevated (27). Free IGF-II (or IGF-I) levels are increased (30), but these measurements are not yet generally available. Endogenous insulin secretion is suppressed appropriately in nonislet cell tumor hypoglycemia.

In a seemingly well individual, the differential diagnosis narrows to two general categories: accidental, surreptitious, or even malicious hypoglycemia and endogenous hyperinsulinism (12–15). Careful consideration of the former possibility (22) should precede a systematic assessment of the latter possibility. Pharmacy errors (*e.g.* substitution of a sulfonylurea for another medication) and medical treatment errors occur (31). Surreptitious hypoglycemia (22, 32–35) is more common in people with knowledge of, and access to, glucose-lowering medications. Malicious hypoglycemia (22, 36, 37) can be accomplished by administration of insulin or an insulin secretagogue.

Clinically, insulinoma is characterized by spells of neuroglycopenia due to endogenous hyperinsulinemic hypoglycemia occurring primarily in the fasting state but occasionally only in the postprandial period (23, 38, 39). The incidence is approximately 1 in 250,000 patient-years (40). It may occur in all ethnic groups and at any age and has a slight predominance in women. Less than 10% of patients have malignant insulinomas, have multiple tumors, or have the multiple endocrine neoplasia, type 1 (MEN-1) syndrome. The recurrence rate after surgical resection is 7% for patients without MEN-1 and 21% for those with MEN-1 (40). Recurrences before 4 yr have elapsed from the initial removal of the tumor suggest fracture of the insulinoma at the time of the original enucleation (41). Long-term survival is the rule for patients who have undergone successful insulinoma removal (40).

The noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is characterized by spells of neuroglycopenia due to endogenous hyperinsulinemic hypoglycemia typically, but not invariably, after a meal (42–45). There is a predominance in men. The pancreatic abnormality is diffuse islet involvement with nesidioblastosis [islet hypertrophy, sometimes with hyperplasia, with enlarged and hyperchromatic β-cell nuclei (46, 47)]. Radiological localization procedures are invariably negative. Confirmation of islet hyperfunction depends on a positive selective arterial calcium stimulation test. Amelioration of symptoms can be expected with partial pancreatectomy guided by the results of the calcium stimulation test. The frequency of NIPHS is much less than that of insulinoma.

Some persons who have undergone Roux-en-Y gastric bypass for obesity have endogenous hyperinsulinemic hypoglycemia most often due to pancreatic islet nesidioblastosis, but occasionally due to an insulinoma (48–50). With nesidioblastosis, spells of neuroglycopenia usually occur in the postprandial period and develop many months after bariatric surgery. Spells of neuroglycopenia that occur in the fasting state soon after bariatric surgery are more likely due to a preexisting insulinoma (51). The predominance of women with post-gastric-bypass hypoglycemia may reflect the gender imbalance of bariatric surgery. The precise mechanisms of hypoglycemia remain to be determined (52–54). The incidence of this disorder is unknown, but at the Mayo Clinic the number of cases exceeds, by a considerable degree, that of insulinoma. Partial pancreatectomy is recommended for nesidioblastosis in patients who do not respond to dietary or medical (*e.g.* an α-glucosidase inhibitor, diazoxide, octreotide) treatments.

Hypoglycemia due to the development of antibodies to native insulin is a rare disorder reported to occur primarily among persons of Japanese or Korean ethnicity (55) and significantly less frequently in Caucasians (56). Persons with this disorder often have a history of autoimmune disease or exposure to sulfhydryl-containing drugs. Symptoms occur in the late postprandial period as insulin secreted in response to the meal and then bound to the circulating antibody dissociates from the antibody in an unregulated fashion. Clues to the diagnosis include very high measured insulin levels during hypoglycemia. That can be the result of an assay artifact caused by the antibody. The severity of hypoglycemia varies from mild, and treatable with lifestyle changes, to severe, for which no modality aside from intragastric glucose infusion has been effective. The diagnosis is readily made by the finding of high titer serum insulin antibodies. A similar hypoglycemic disorder has been described in patients who have a high capacity insulin binding monoclonal paraprotein (57).

Evaluation of hypoglycemia in seemingly well individuals

If a seemingly well patient is symptomatic when seen by the caregiver, the most expeditious diagnostic maneuver (14, 15) is to obtain plasma for the measurement of glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and circulating oral hypoglycemic agents (ideally all available sulfonylureas and glinides), and then to correct the hypoglycemia with the injection of 1.0 mg glucagon iv with measurement of the plasma glucose response. These data will distinguish endogenous (and exogenous) hyperinsulinism from other causes of hypoglycemia. Insulin antibodies, which need not be measured at the time of hypoglycemia, will identify insulin autoimmune hypoglycemia.

The key pathophysiological feature of endogenous hyperinsulinism is the failure of insulin secretion to fall to very low rates as plasma glucose concentrations fall to hypoglycemic levels; hypoglycemia is the result of low rates of glucose production rather than high rates of glucose utilization (58). Thus, plasma insulin, C-peptide, and proinsulin concentrations need not be high relative to normal euglycemic values but only inappropriately high in the setting of low fasting plasma glucose concentrations (12–15). Critical diagnostic findings are plasma insulin concentrations of at least 3 μU/ml (18 pmol/liter), plasma C-peptide concentrations of at least 0.6 ng/ml (0.2 nmol/liter), and plasma proinsulin concentrations of at least 5.0 pmol/liter when the fasting plasma glucose concentrations are below 55 mg/dl

(3.0 mmol/liter) (14, 15). Ratios employing insulin and glucose have no diagnostic utility (59). These criteria assume the absence of intercurrent illnesses including renal insufficiency.

An occasional patient with an insulinoma may not fulfill these criteria even during a 72-h fast (15, 60), and a few have plasma insulin levels below 3 μU/ml (18 pmol/liter) during fasting hypoglycemia, but plasma C-peptide levels are usually 0.6 ng/ml (0.2 mmol/liter) or greater and plasma proinsulin levels are usually 5.0 pmol/liter or greater in the latter patients. For example, in one series the plasma insulin criterion was met in 29 of 32 patients with an insulinoma, whereas the C-peptide and proinsulin criteria were met in all 32 patients (61). Plasma β-hydroxybutyrate levels of 2.7 mmol/liter or less and an increase in the plasma glucose concentration of at least 25 mg/dl (1.4 mmol/liter) after iv glucagon, the latter indicating preserved hepatic glycogen stores, provide biological evidence of insulin (or IGF) excess (62). The findings that distinguish among the causes of hyperinsulinemic (or IGF-mediated) hypoglycemia are summarized in Table 3.

When Whipple's triad has not been documented in a patient with a history of suggestive spells and when the appropriate tests have not been obtained during an episode of spontaneous hypoglycemia, recreation of the circumstances likely to lead to hypoglycemia should be pursued (12, 14, 15). For the patient with a history suggesting fasting hypoglycemia, this may be accomplished by withholding food, and for the patient with a history suggestive of postprandial hypoglycemia, this may be accomplished by providing the type of meal likely to cause a spell. When these maneuvers fail, the patient with suspected fasting hypoglycemia should undergo a prolonged supervised fast. This fast can be initiated as an outpatient and completed (if necessary) in hospital. The fast should be continued to the point at which Whipple's triad is documented or to a plasma glucose of less than 55 mg/dl (3.0 mmol/liter) if Whipple's triad had been documented unequivocally previously (15, 60), unless a progressive rise in β-hydroxybutyrate levels signals a negative fast (62). Plasma glucose concentrations should be measured with a precise method, not with self-monitoring of blood glucose. Most, but not all (60), patients with an insulinoma fulfill these diagnostic criteria in less than 72 h. Indeed, that occurs in less than 24 h in about two thirds, and in less than 48 h in the vast majority, of affected patients (60). The patient with a history suggestive of postprandial hypoglycemia should undergo a mixed-meal test. That meal should include the components recognized by the patient as likely to cause hypoglycemia (although a nutritional supplement formula mixed meal is sometimes used) and should be conducted over 5 h. An oral glucose tolerance test should never be used for the evaluation of suspected postprandial hypoglycemia (63). However, standards for the interpretation of the mixed-meal test have not been established. Current clinical usage is to apply the above criteria developed under fasting conditions (14) to the results from a mixed-meal challenge. Finally, for the patient requiring iv glucose to prevent hypoglycemia, diagnostic data can be obtained by serial sampling, under close supervision, after temporary discontinuation of glucose infusion.

A patient with documented Whipple's triad, inappropriately high plasma insulin, C-peptide, and proinsulin levels; and no

TABLE 3. Patterns of findings during fasting or after a mixed meal in normal individuals with no symptoms or signs despite relatively low plasma glucose concentrations (*i.e.* Whipple's triad not documented) and in individuals with hyperinsulinemic (or IGF-mediated) hypoglycemia or hypoglycemia caused by other mechanisms

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/ml)	C-peptide (nmol/liter)	Proinsulin (pmol/liter)	β-Hydroxybutyrate (mmol/liter)	Glucose increase after glucagon (mg/dl)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[a]	≫5[a]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[b]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

Neg, Negative; Pos, positive; PGBH, post gastric bypass hypoglycemia.

[a] Free C-peptide and proinsulin concentrations are low.

[b] Increased pro-IGF-II, free IGF-II, IGF-II/IGF-I ratio.

detectable oral hypoglycemic agent levels during fasting hypoglycemia; and no circulating antibodies to insulin probably has an insulinoma (12–15). Nonetheless, accidental, surreptitious, or malicious hypoglycemias are difficult entities to diagnose. These diagnoses depend on a high degree of clinical suspicion and pursuit of potential sources of offending agents (including inspection of the patient's medications). There are, however, causes of fasting endogenous hyperinsulinemic hypoglycemia other than an insulinoma. Some patients do not have an insulinoma but have a diffusely expanded islet cell mass (46, 47, 64, 65). That is often termed nesidioblastosis, although the histological finding of islets budding from pancreatic ducts is not invariably present (46, 47). Nesidioblastosis due to prolonged factitious use of a sulfonylurea has been reported (66). Although seemingly convincing cases have been reported (see Ref. 67), ectopic insulin secretion must be very rare. Similarly, hyperinsulinemic hypoglycemia linked to a mutation of the insulin receptor (68) and exercise-induced hyperinsulinemia (69) are rare syndromes. Finally, rare patients with fasting hypoglycemia and appropriately suppressed C-peptide levels but inappropriately elevated insulin levels have an agonist antibody to the insulin receptor (70). In that instance hypoglycemia is the result of the action of the antibody to stimulate insulin receptors; somewhat elevated insulin levels are thought to be the result of decreased clearance of insulin. Typically, the affected patient is African-American, usually female, often with an associated autoimmune disease.

The diagnosis of an insulinoma requires convincing clinical and biochemical evidence before any attempt to regionalize or localize the tumor (12–15). Although the results with a given method reflect the experience and expertise with that method at a given center, computed tomography, MRI, and transabdominal ultrasonography detect most insulinomas (71–73). They also often detect metastases in the less than 10% of insulinomas that are malignant. However, because insulinomas are often less than 1.0 cm in diameter (73), negative imaging does not exclude an insulinoma. Computed tomography detects 70 to 80% and MRI about 85% (73). Somatostatin receptor scintigraphy is reported to detect insulinomas in approximately half of affected patients (74), although a sensitivity of 80% has been reported (75). Endoscopic pancreatic ultrasonography, with the option of fine-needle aspiration of a detected tumor, is invasive but in some centers has a sensitivity greater than 90% (76, 77). With the combination of noninvasive and selected invasive modalities (particularly endoscopic ultrasound), most insulinomas are localized preoperatively (72, 78). Selective pancreatic arterial calcium injections, with an endpoint of a greater than 2-fold increase in hepatic venous insulin levels over baseline (79, 80) [or perhaps a greater than 5-fold increase with contemporary specific insulin assays (81)] regionalizes insulinomas with high sensitivity (81, 82). That invasive procedure can help to regionalize an insulinoma when imaging is equivocal or negative. However, it is the procedure of choice for confirming noninsulinoma pancreatogenous hypoglycemia (15, 43–45) and post Roux-en-Y gastric bypass hypoglycemia (48–50) because standard imaging is negative in those disorders. The relative utility of positron emission tomography in the noninvasive localization of insulinomas remains to be determined, although that with [^{18}F]dihydroxyphenylalanine is promising (83). Intraoperative pancreatic ultrasonography almost invariably localizes tumors that are not apparent to the experienced pancreatic surgeon.

Prevention of recurrent hypoglycemia requires treatment that corrects or circumvents the hypoglycemic mechanism (12–15) (Table 1). Offending drugs can be discontinued or their dosage reduced. Underlying critical illnesses can often be treated. Cortisol can be replaced. Surgical, radiotherapeutic, or chemotherapeutic reduction of the mass of a nonislet cell tumor can alleviate hypoglycemia even if the tumor cannot be cured; glucocorticoid, GH, or occasionally octreotide administration may alleviate hypoglycemia in such patients. Surgical resection of a benign insulinoma is curative. Medical treatment with diazoxide, octreotide, or both can be used if resection of an insulinoma is not possible and in patients with a nontumor β-cell disorder, although partial pancreatectomy may be required. Treatment of autoimmune hypoglycemias (*e.g.* with a glucocorticoid or another immunosuppressant medication) is problematic, but these disorders may be self-limited, at least in Asians. In patients with NIPHS or post gastric bypass hypoglycemia medical therapy with frequent feedings, an α-glucosidase inhibitor, diazoxide, and octreotide are occasionally effective. Partial pancreatectomy often provides amelioration. Failing these treatments, provision of exogenous glucose with large doses of uncooked cornstarch or even intragastric glucose infusion may be necessary.

2.1 Values

The decision to undergo invasive localization procedures and partial pancreatectomy places a higher value on achieving long-term remission of hypoglycemia and a lower value on avoiding invasive diagnostic procedures and avoiding the potential downsides of pancreatectomy (including diabetes, bleeding, infection, and death). Some patients with mild hypoglycemia who are able to cope with minimal interventions may prefer to avoid invasive evaluations and surgery. Severely affected patients may prefer a treatment approach that includes precise localization of the insulin-producing lesion and partial pancreatectomy.

2.1 Remarks

Suggested protocols for a prolonged diagnostic fast and for a mixed-meal diagnostic test are shown in Tables 4 and 5, respectively.

3.0 Evaluation and Management of Hypoglycemia in Persons with Diabetes Mellitus

Background

Treatment-induced hypoglycemia is the limiting factor in the glycemic management of diabetes (12, 16, 84). It causes recurrent morbidity in most persons with type 1 diabetes mellitus (T1DM) and in many with advanced (*i.e.* absolute endogenous insulin-deficient) type 2 diabetes mellitus (T2DM), and it is

TABLE 4. Suggested protocol for a prolonged diagnostic fast

Date the onset of the fast as the time of the last food intake. Discontinue all nonessential medications.
Allow the patient to drink calorie-free beverages. Ensure that the patient is active during waking hours.
Collect samples for plasma glucose, insulin, C-peptide, proinsulin, and β-hydroxybutyrate every 6 h until the plasma glucose concentration is less than 60 mg/dl (3.3 mmol/liter); at that point the frequency of sampling should be increased to every 1 to 2 h.
Samples for plasma insulin, C-peptide, and proinsulin should be sent for analysis only in those samples in which the plasma glucose concentration is less than 60 mg/dl (3.3 mmol/liter).
End the fast when the plasma glucose concentration is less than 45 mg/dl (2.5 mmol/liter) and the patient has symptoms and/or signs of hypoglycemia (or if 72 h have elapsed without symptoms). The decision to end the fast before 72 h should not be based on a low plasma glucose concentration alone, in the absence of symptoms or signs, because some healthy individuals, especially women and children, have low glucose levels during prolonged fasting. Alternatively, the fast can be ended when the plasma glucose concentration is less than 55 mg/dl (3.0 mmol/liter) without symptoms or signs if Whipple's triad was documented unequivocally on a prior occasion.
A low plasma glucose concentration is a necessary, albeit not in itself sufficient, finding for the diagnosis of hypoglycemia. Therefore, the decision to end the fast should be based on laboratory-measured plasma glucose concentrations, not those estimated with a point-of-care glucose monitor. If it is judged necessary to treat urgently because of severe symptoms, obtain samples for all of the following before administering carbohydrates.
At the end of the fast, collect samples for plasma glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate, and oral hypoglycemia agents, and then inject 1.0 mg of glucagon iv and measure plasma glucose 10, 20, and 30 min later. (Insulin antibodies should be measured, but not necessarily during hypoglycemia.)

TABLE 5. Suggested protocol for a mixed-meal diagnostic test

Perform the test after an overnight fast. Hold all nonessential medications.
Use a mixed meal similar to that which the patient reports has caused symptoms (or use a commercial formula mixed meal).
Collect samples for plasma glucose, insulin, C-peptide, and proinsulin before ingestion and every 30 min through 300 min after ingestion of the meal.
Observe the patient for symptoms and/or signs of hypoglycemia and ask the patient to keep a written log of all symptoms, timed from the start of meal ingestion. If possible, avoid treatment until the test is completed.
A low plasma glucose concentration is a necessary, albeit not in itself sufficient, finding for a diagnosis of hypoglycemia. Therefore, the mixed-meal test should be interpreted on the basis of laboratory-measured plasma glucose concentrations, not those estimated with a point-of-care glucose monitor. If it is judged necessary to treat before 300 min because of severe symptoms, obtain samples for all of the following before administering carbohydrates.
Samples for plasma insulin, C-peptide, and proinsulin should be sent for analysis only in those samples in which plasma glucose is less than 60 mg/dl (3.3 mmol/liter), and a sample for measurement of oral hypoglycemic agents should be obtained, if Whipple's triad is demonstrated. In that case, antibodies to insulin should also be measured.

sometimes fatal. It precludes maintenance of euglycemia over a lifetime of diabetes and thus full realization of the established microvascular and potential macrovascular and other benefits of long-term glycemic control. It compromises physiological and behavioral defenses against subsequent falling plasma glucose concentrations and thus causes a vicious cycle of recurrent hypoglycemia. Because of steady improvements in the glycemic management of diabetes, it is possible both to improve glycemic control and to minimize the risk of hypoglycemia in many patients (12, 16, 84–86). Nonetheless, the problem of hypoglycemia has not been solved. Solution of that problem will require glucose-regulated insulin replacement or secretion until the prevention and cure of diabetes is achieved (16).

Hypoglycemia in diabetes is fundamentally the result of treatments that raise insulin levels and thus lower plasma glucose concentrations (12, 16, 84, 85). Those treatments include insulin or insulin secretagogues such as a sulfonylurea or a nonsulfonylurea insulin secretagogue (*e.g.* nateglinide or repaglinide). Early in its course, T2DM may respond to drugs that do not raise insulin levels at normal or low plasma glucose concentrations and, therefore, should not cause hypoglycemia. Those include a biguanide (metformin), which nonetheless has been reported to cause hypoglycemia (87); thiazolidinediones (pioglitazone, rosiglitazone); α-glucosidase inhibitors (acarbose, miglitol); glucagon-like peptide-1 receptor agonists (exenatide, liraglutide); and dipeptidyl peptidase-IV inhibitors (sitagliptin, vildagliptin). However, these drugs can increase the risk of hypoglycemia when used with an insulin secretagogue (see Ref. 88) or insulin.

Physiology and pathophysiology

Hypoglycemia is typically the result of the interplay of relative or absolute therapeutic insulin excess and compromised physiological and behavioral defenses against falling plasma glucose concentrations in T1DM and long-standing T2DM (12, 16, 84, 85).

Relative, or even absolute, insulin excess must occur from time to time during treatment with an insulin secretagogue or insulin because of the pharmacokinetic imperfections of these therapies. Insulin excess of sufficient magnitude can, of course, cause hypoglycemia. Nonetheless, as discussed below, the incidence of hypoglycemia is relatively low (at least with current glycemic goals), even during treatment with insulin, early in the course of T2DM when glycemic defenses are intact. However, the risk increases progressively over time and approaches that in T1DM as glycemic defenses become compromised.

As discussed earlier, the critical physiological defenses against falling plasma glucose concentrations include: 1) decrements in insulin secretion; 2) increments in glucagon secretion; and, in the absence of the latter, 3) increments in epinephrine secretion (6, 7, 12). The behavioral defense is the ingestion of carbohydrates (6, 7, 12). That behavior is prompted by the perception of symptoms, largely the neurogenic symptoms (4) mediated by sympathetic neural activation (5).

All of these defenses, not just insulin secretion, are compromised in T1DM and in long-standing T2DM (12, 16, 89, 90). In fully developed T1DM, circulating insulin levels do not decrease as plasma glucose levels decline. Furthermore, in the absence of a β-cell signal, including a decrease in intraislet insulin (91), the α-cell glucagon response to hypoglycemia is also lost (92). In the absence of the first (insulin) and second (glucagon) defenses,

persons with T1DM are critically dependent on the third defense, epinephrine secretion. However, the epinephrine response to hypoglycemia is often attenuated (8, 12, 16, 89, 93, 94). Through mechanisms yet to be clearly defined but generally thought to reside in the brain (12, 16, 85, 95), the glycemic threshold for sympathoadrenal activation is shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia, as well as by prior exercise and by sleep (12, 16, 89, 90, 95–97). In the setting of absent decrements in insulin and absent increments in glucagon as plasma glucose levels fall in response to therapeutic hyperinsulinemia, the attenuated epinephrine response causes the clinical syndrome of defective glucose counterregulation that has been shown to increase the risk of severe hypoglycemia by 25-fold (98) or even more (99). In addition, the attenuated sympathetic neural response causes the clinical syndrome of hypoglycemia unawareness—impairment or even loss of the warning symptoms that previously prompted the behavioral defense, *i.e.* the ingestion of carbohydrates. Hypoglycemia unawareness is associated with a 6-fold increased risk for severe hypoglycemia (100).

The concept of hypoglycemia-associated autonomic failure (HAAF) in diabetes is based on pivotal findings in nondiabetic individuals (97) and patients with T1DM (101) and was first documented in T1DM (89). It posits that recent antecedent hypoglycemia [or prior exercise or sleep (16)] causes both defective glucose counterregulation (by reducing the epinephrine response in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (largely by reducing the sympathetic neural response and the resulting neurogenic symptoms) and, thus, a vicious cycle of recurrent hypoglycemia (12, 16). Perhaps the most compelling support for the clinical impact of HAAF in T1DM is the finding that as little as 2–3 wk of scrupulous avoidance of treatment-induced hypoglycemia reverses hypoglycemia unawareness, and improves the reduced epinephrine component of defective glucose counterregulation in most affected patients (102–105).

More recently, the concept of HAAF (12, 16, 89) has been extended to patients with long-standing T2DM and absolute insulin deficiency (90). As just discussed, HAAF stems fundamentally from β-cell failure. Initially, T2DM is characterized by insulin resistance and only relative hypoinsulinemia, conditions that allow decrements in insulin and increments in glucagon while plasma glucose concentrations fall. Over time, however, absolute endogenous insulin deficiency develops (87). Thus, as patients approach the insulin-deficient end of the spectrum of T2DM (118), typically over many years, their insulin and glucagon responses to falling glucose levels are lost (90), as in T1DM. Furthermore, their glycemic thresholds for sympathoadrenal responses are shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia (90), as in T1DM. Thus, patients with long-standing T2DM are also at risk for HAAF.

There may well be as yet unrecognized functional, and thus potentially reversible, causes of a reduced sympathoadrenal response to hypoglycemia, the key feature of HAAF, in addition to recent antecedent hypoglycemia, prior exercise, and sleep. There may also be a structural, irreversible component. For example, the reduced sympathoadrenal response to hypoglycemia is not fully normalized after scrupulous avoidance of hypoglycemia (103–105) or during insulin independence after successful pancreatic islet transplantation (106). Furthermore, the sympathoadrenal response to hypoglycemia is reduced to a greater extent in patients with classical diabetic autonomic neuropathy (107, 108). Finally, a reduced plasma metanephrine response to hypoglycemia in patients with HAAF suggests a reduced adrenomedullary epinephrine secretory capacity (109). Such a structural component would be consistent with the evidence of a relationship between severe hypoglycemia and a long duration of T1DM (see Ref. 110).

In summary, although the pathophysiology of glucose counterregulation is the same in T1DM and T2DM, it develops rapidly in T1DM (as absolute insulin deficiency develops rapidly) but slowly in T2DM (as absolute insulin deficiency develops slowly). This difference in the time course of the evolution of HAAF plausibly explains, at least in part, the relatively low frequency of treatment-induced hypoglycemia early in the course of T2DM and the higher frequency of treatment-induced hypoglycemia, approaching that in T1DM, later in T2DM (discussed below). That pathophysiology also provides insight into the risk factors for, and the prevention of, hypoglycemia in T2DM as well as in T1DM.

Incidence and impact

Hypoglycemia is a fact of life for most persons with T1DM (12, 16). The average patient with T1DM suffers two episodes of symptomatic hypoglycemia per week—thousands of such episodes over a lifetime of diabetes—and one episode of temporarily disabling hypoglycemia, often with seizure or coma, per year. An estimated 2–4% of people with T1DM die from hypoglycemia (12, 111).

Reported severe hypoglycemia event rates in patients with T1DM (119–123) and those with T2DM (119–121, 124–131) are summarized in Table 6.

Although prolonged, profound hypoglycemia can cause neurological damage and thus brain death, the mechanism(s) of sudden death during less marked hypoglycemia is unknown but may involve a cardiac arrhythmia (6). Hypoglycemia causes a transiently prolonged corrected QT interval, as well as increased QT dispersion, an effect thought to be mediated by the sympathoadrenal response to hypoglycemia (112, 113). Furthermore, a prolonged corrected QT interval has been found to be associated with episodes of nocturnal hypoglycemia in patients with T1DM (114, 115). Thus, it is reasonable to suggest (112–115) that a fatal arrhythmia triggered by hypoglycemia might explain the "dead in bed syndrome," an unexpected death of a person with T1DM occurring during the night (116).

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, 10,251 patients with T2DM at high cardiovascular risk (but with no history of frequent or recent serious hypoglycemic events) were randomized to either intensive glycemic therapy with an HbA_{1C} goal of less than 6.0% or to standard glycemic therapy (117). After a median follow-up of 3.4 yr, with stable median HbA_{1C} levels of 6.4 and 7.5%, respectively, intensive glycemic therapy was discontinued because 5.0% of the

patients in the intensive therapy group, compared with 4.0% of those in the standard therapy group, had died (hazard ratio, 1.22; 95% confidence interval, 1.01–1.46; $P = 0.04$). The cause of excess mortality during intensive glycemic therapy in ACCORD is not known (117). It could have been chance. It could have been the result of a nonglycemic effect of the intensive therapy regimen (*e.g.* an adverse effect of one or more of the drugs, weight gain, or something else) although none was apparent. Nonetheless, the most plausible cause of excess mortality during intensive therapy in ACCORD is iatrogenic hypoglycemia: 1) median glycemia (HbA_{1C}) was intentionally and demonstrably lower in the intensive glycemic therapy group; 2) lower HbA_{1C} levels are known to be associated with a higher frequency of hypoglycemia in T2DM (117, 132); indeed, the prevalence of severe hypoglycemia was more than 3-fold higher in the intensive therapy group in ACCORD (117); 3) hypoglycemia can be fatal in T2DM (6); that includes sudden, presumably cardiac arrhythmic, death; and 4) more patients died in the intensive glycemic therapy group (117). Another randomized controlled trial of aggressive glycemic therapy in T2DM, the VA Diabetes Trial was reported at the 2008 American Diabetes Association (ADA) meeting. The incidence of severe hypoglycemia was higher in the intensively treated group, and a history of severe hypoglycemia was a significant predictor of cardiovascular death.

Overall, hypoglycemia is less frequent in T2DM than in T1DM (12, 16). However, hypoglycemia becomes progressively more limiting to glycemic control over time in T2DM (118). The UK Hypoglycemia Study Group reported that in patients with T2DM treated with insulin for less than 2 yr or more than 5 yr, the prevalence of severe hypoglycemia was 7 and 25%, and the incidence was 10 and 70 episodes per 100 patient-years, respectively (119). The pattern for self-treated hypoglycemia was similar (119). Thus, whereas the risk of hypoglycemia is relatively low in the first few years of insulin treatment, that risk increases substantially later in the course of T2DM.

Reported hypoglycemia event rates in diabetes are generally underestimates because of the difficulty of ascertainment. Asymptomatic episodes of hypoglycemia will be missed unless incidentally detected by routine self-monitoring of blood glucose or by continuous glucose sensing. Furthermore, symptomatic episodes may not be recognized as such because the symptoms of hypoglycemia are nonspecific. Even if they are recognized, they are often not long remembered and therefore may not be reported at periodic clinic visits. Severe hypoglycemic episodes—those sufficiently disabling that they require the assistance of another person—are more dramatic events that are more likely to be recalled (by the patient or by a close associate). Thus, although they represent only a small fraction of the total hypoglycemic experience, estimates of severe hypoglycemia event rates are the most reliable. In addition, hypoglycemia event rates determined prospectively, particularly if hypoglycemia is a primary study endpoint, should be more reliable than those determined retrospectively. Although the incidence of hypoglycemia (Table 6) is often determined from clinical treatment trials, there are limitations to that approach. First, hypoglycemia is not a primary outcome of such trials, and therefore the extent of data collection concerning hypoglycemia varies. For example, much was learned about hypoglycemia in T1DM in the Diabetes Control and Complications Trial (133), but the hypoglycemia event rates in T2DM in the United Kingdom Prospective Diabetes

TABLE 6. Event rates for severe hypoglycemia (requiring the assistance of another person) expressed as episodes per 100 patient-years

First author, year (Ref.)	n	Event rate	Comment
T1DM			
UK Hypoglycaemia Study Group, 2007 (119)	57[a]	320	Prospective multicenter study
	50[b]	110	
MacLeod, 1993 (120)	544	170	Retrospective clinic survey, randomly selected sample
Donnelly, 2005 (121)	94	115	Prospective study, population-based random sample
Reichard and Pihl, 1994 (122)	48	110	Clinical trial, intensive insulin group
DCCT Research Group, 1993 (123)	711	62	Clinical trial, intensive insulin group
T2DM			
MacLeod, 1993 (120)	56	73	Retrospective clinic survey, randomly selected sample
UK Hypoglycaemia Study Group, 2007 (119)	77[c]	70	Prospective multicenter study
	89[d]	10	
Akram, 2006 (124)	401	44	Retrospective clinic survey
Donnelly, 2005 (121)	173	35	Prospective study, population-based random sample
Henderson, 2003 (125)	215	28	Retrospective clinic survey, randomly selected sample
Murata, 2005 (126)	344	21	Prospective study, random Veterans Affairs sample
Saudek, 1996 (127)	62	18[e]	Clinical trial, multiple insulin injection group
Gürlek, 1999 (128)	114	15	Retrospective clinic survey
Abraira, 1995 (129)	75	3	Clinical trial, intensive insulin group
Yki-Järvinen, 1999 (130)	88	0	Clinical trial, initial insulin therapy
Ohkubo, 1995 (131)	52	0	Clinical trial, initial insulin therapy

Studies covering at least 1 yr, involving at least 48 patients, and reporting severe hypoglycemia event rates are included.

[a] Insulin treatment for >15 yr.

[b] Insulin treatment for <5 yr.

[c] Insulin treatment for >5 yr.

[d] Insulin treatment for <2 yr.

[e] Definite (8 per 100 patient-years) plus suspected (10 per 100 patient-years).

Study are not known (132). Second, insulin treatment trials in T2DM are often conducted in patients just failing oral hypoglycemic agent therapy and naive to insulin therapy. Such patients are at relatively low risk for hypoglycemia as discussed earlier. Third, the therapeutic goals in clinical trials are often different from those agreed upon between patients and health care providers in clinical practice. Thus, it is important to consider evidence from prospective, population-based studies focused on hypoglycemia.

The population-based, prospective study of Donnelly *et al.* (121) indicates that the overall hypoglycemia event rates in insulin-treated patients with T2DM are approximately one third of those in patients with T1DM. The rates for any hypoglycemia were approximately 4300 per 100 patient-years in T1DM and approximately 1600 per 100 patient-years in T2DM. The rates for severe hypoglycemia were 115 per 100 patient-years in T1DM and 35 per 100 patient-years in T2DM. Furthermore, in population-based studies from hospital regions with known T1DM and T2DM incidences, event rates for severe hypoglycemia requiring emergency medical treatment in insulin-treated T2DM were approximately 40% (134) and approximately 100% (135) of those in T1DM. Because the prevalence of T2DM is approximately 20-fold greater than that of T1DM and because many patients with T2DM ultimately require treatment with insulin, these data suggest that most episodes of hypoglycemia, including severe hypoglycemia, occur in persons with T2DM.

Recommendation

3.1 We suggest that persons with diabetes become concerned about the possibility of developing hypoglycemia when the self-monitored blood glucose concentration is falling rapidly or is no greater than 70 mg/dl (3.9 mmol/liter) (2⊕○○○).

3.1 Evidence

The ADA Workgroup on Hypoglycemia recommended that persons with drug-treated diabetes become concerned about developing hypoglycemia at a plasma glucose concentration of 70 mg/dl (3.9 mmol/liter) or less (136). That value approximates the lower limit of the postabsorptive plasma glucose concentration range and the glycemic threshold for activation of physiological glucose counterregulatory mechanisms (7), and it is low enough to reduce glycemic defenses against subsequent hypoglycemia (137) in nondiabetic individuals. It is higher than the glucose levels required to produce symptoms of hypoglycemia [~55 mg/dl (3.0 mmol/liter)] or to impair brain function in nondiabetic individuals (6, 7) and substantially higher than those that do so in persons with well-controlled diabetes (6–8), although persons with poorly controlled diabetes sometimes become symptomatic at somewhat higher glucose levels (8, 9). Thus, use of a 70 mg/dl (3.9 mmol/liter) plasma glucose cutoff generally gives the patient time to take action to prevent a symptomatic hypoglycemic episode. Also, in practice, self-monitoring of blood glucose is usually done with devices that are not precise analytical instruments, particularly at low plasma glucose levels (138), and the recommended cutoff value provides some margin for their inaccuracy. The ADA Workgroup also recommended a classification of hypoglycemia—severe, documented symptomatic, asymptomatic, probable symptomatic, and relative hypoglycemia—in diabetes (136) (Table 7).

TABLE 7. ADA Workgroup on Hypoglycemia classification of hypoglycemia in persons with diabetes (136)

Severe hypoglycemia. An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
Documented symptomatic hypoglycemia. An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤70 mg/dl (3.9 mmol/liter).
Asymptomatic hypoglycemia. An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dl (3.9 mmol/liter).
Probable symptomatic hypoglycemia. An event during which symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤70 mg/dl [3.9 mmol/liter]).
Relative hypoglycemia. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, with a measured plasma glucose concentration >70 mg/dl (3.9 mmol/liter) but approaching that level.

Persons with diabetes typically track their glucose levels with intermittent self-monitoring of blood glucose. However, that provides a glucose estimate at only one point in time and therefore does not indicate whether glucose levels are rising, stable, or falling toward hypoglycemia. That problem is being addressed by the development of technologies for continuous glucose sensing. Those technologies are as yet only evolving (139–142). It is hoped that they will lead to closed-loop insulin replacement in the not too distant future (143). Nonetheless, although these devices are promising, compelling evidence that they reliably assist patients in preventing hypoglycemia is needed.

Recommendation

3.2 Given the established long-term microvascular benefits of glycemic control, we recommend that the therapeutic glycemic goal be the lowest mean glycemia (*e.g.* HbA_{1C}) that can be accomplished safely in a given patient at a given point in the progression of that individual patient's diabetes (1⊕⊕⊕⊕).

3.2 Evidence

Randomized controlled trials have established that intensive glycemic therapy prevents or delays the microvascular complications—retinopathy, nephropathy, and neuropathy—of diabetes (122, 123, 131, 144, 145), albeit at the expense of an increased frequency of hypoglycemia (117, 118, 122, 123, 132, 133, 144, 145). It also appears to reduce the frequency of macrovascular complications in T1DM (146, 147). Recent relatively short-term randomized controlled trials have not demonstrated a macrovascular benefit of intensive glycemic therapy in T2DM (117, 148). However, they do not exclude that possibility if glycemic control could be accomplished safely over a longer

period of time. In any event, given the established microvascular benefit of improved glycemic control (122, 123, 131, 144, 145, 148), the recommendation that plasma glucose levels be held as close to the nondiabetic range as safely possible in persons with diabetes (123) is now generally accepted (149). For example, the ADA recommends an HbA_{1C} level as low as can be accomplished safely in an individual patient and generally below 7.0% (150). Nonetheless, there is substantial long-term benefit from reducing HbA_{1C} from higher to lower levels, although still above recommended levels (151, 152). However, the caregiver should be concerned about the possibility of hypoglycemia in a patient with an unusually low HbA_{1C}.

3.2 Values

Obviously, the practical difficulty here is the qualifier *safely*. The recommended glycemic goal of near euglycemia is a compromise necessitated by the barrier of treatment-induced hypoglycemia. With currently available treatments, including insulin, that goal can be accomplished with some degree of safety [*i.e.* the absence of severe hypoglycemia (Table 7)] in many patients, albeit with considerable patient and caregiver effort and expense. In other patients with T1DM or T2DM, it cannot be accomplished safely. Furthermore, some patients place a very high value on avoiding hypoglycemia. Thus, glycemic goals need to be individualized (149, 150). Nonetheless, the reality or the possibility of hypoglycemia should not be used as an excuse for poor glycemic control in persons with diabetes.

Recommendation

3.3 We recommend that the prevention of hypoglycemia in diabetes involve addressing the issue in each patient contact and, if hypoglycemia is a problem, making adjustments in the regimen based on review and application of the principles of intensive glycemic therapy—diabetes self-management (supported by education and empowerment), frequent self-monitoring of blood glucose, flexible and appropriate insulin or insulin secretagogue regimens, individualized glycemic goals, and ongoing professional guidance and support—and consideration of each of the known risk factors for hypoglycemia (1⊕⊕⊕○).

3.3 Evidence

It is, of course, preferable to prevent, rather than to treat, hypoglycemia in persons with diabetes. Because prevention of hypoglycemia, as compared with a reactive approach, is much more likely to avoid serious adverse effects of recurrent episodes of hypoglycemia, we upgraded the quality of the evidence in support of this recommendation, which starts as low, to moderate. The prevention of hypoglycemia requires the practice of hypoglycemia risk factor reduction (12, 16, 85): 1) acknowledging the problem; 2) applying the principles of aggressive glycemic therapy of diabetes; 3) considering the conventional risk factors (Table 8); and 4) considering the risk factors indicative of HAAF in diabetes (Table 8).

First, the issue of hypoglycemia should be addressed in every contact with patients with drug-treated diabetes, particularly those treated with an insulin secretagogue or insulin. Patient concerns about the reality, or the possibility, of hypoglycemia can be a barrier to glycemic control. It is also helpful to seek input from close associates of the patient because they may have observed clues to episodes of hypoglycemia not recognized by the patient. Even if no concerns are expressed, critical examination of the self-monitoring of blood glucose record (or continuous glucose sensing data), preferably by downloading the data, may disclose that hypoglycemia is a problem.

TABLE 8. Risk factors for hypoglycemia in diabetes

Conventional risk factors–relative or absolute insulin excess
1. Insulin or insulin secretagogue doses are excessive, ill-timed, or of the wrong type.
2. Exogenous glucose delivery is decreased (*e.g.* after missed meals and during the overnight fast).
3. Glucose utilization is increased (*e.g.* during exercise).
4. Endogenous glucose production is decreased (*e.g.* after alcohol ingestion).
5. Sensitivity to insulin is increased (*e.g.* after weight loss, an increase in regular exercise or improved glycemic control, and in the middle of the night).
6. Insulin clearance is decreased (*e.g.* with renal failure).

Risk factors for hypoglycemia-associated autonomic failure
1. Absolute endogenous insulin deficiency.
2. A history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise, and sleep.
3. Aggressive glycemic therapy *per se* (lower HbA_{1C} levels, lower glycemic goals, or both).

Second, if hypoglycemia is a problem, the principles of intensive glycemic therapy should be considered and applied. These principles include: 1) diabetes self-management (supported by education and empowerment); 2) frequent self-monitoring of blood glucose (and perhaps in some instances continuous glucose sensing); 3) flexible and appropriate insulin (and other drug) regimens; 4) individualized glycemic goals; and 5) ongoing professional guidance and support.

Diabetes self-management (supported by education and empowerment) is fundamentally important (153, 154). As the therapeutic regimen becomes progressively more complex—early in T1DM and later in T2DM—the success of glycemic management becomes progressively more dependent on the management decisions and skills of a well-informed patient. In addition, frequent self-monitoring of blood glucose data can reasonably be expected to provide insight leading to rational modifications of the therapeutic regimen (141), although additional critical evidence on that point is needed. The emerging technology of continuous glucose sensing is conceptually attractive, but its clinical utility has not been documented (155–158). As in T1DM, in T2DM the use of long-acting basal (glargine, detemir) and rapid-acting prandial (lispro, aspart, glulisine) insulin analogs can at least minimize the risk of nocturnal hypoglycemia (159–162). Indeed, recent systematic reviews have concluded that the use of long-acting basal insulin analogs reduces the incidence of overall, symptomatic, and nocturnal hypoglycemia in T2DM and T1DM (159–161), and the use of rapid-acting prandial insulin analogs reduces nocturnal hypoglycemia in T1DM (159).

Based on their experience and knowledge of the literature, some authorities have concluded that continuous sc insulin infusion (CSII) with a rapid-acting insulin analog both improves

glycemic control and reduces the rate of severe hypoglycemia compared with multiple daily injection (MDI) insulin therapy (see Ref. 163). A recent systematic review of 15 randomized trials (13 in T1DM) comparing CSII with MDI, published since 2002 and conducted mostly in patients with elevated end-of-study HbA_{1C} levels, found statistical trends favoring CSII but no clear clinical benefits of using CSII rather than MDI in terms of mild, nocturnal, or severe hypoglycemia in T1DM and T2DM (164).

Among the commonly used sulfonylureas, glyburide (glibenclamide) is most often associated with hypoglycemia (165, 166).

With respect to glycemic goals, the generic goal is an HbA_{1C} level as low as can be accomplished safely (150). Nonetheless, as mentioned earlier, there is substantial long-term benefit from reducing HbA_{1C} from higher to lower, although still above recommended, levels (151, 152). Again, glycemic goals should be individualized (149, 150).

Ongoing professional guidance and support are best provided in a chronic care model, a system of long-term diabetes care that differs fundamentally from the traditional more or less acute care model of occasional physician outpatient visits (155, 167). Such a system is organized and conducted by a diabetes care team that includes, in addition to a physician, professionals trained in, and dedicated to, translation of the ever-evolving principles of contemporary diabetes care into practical diabetes management in individual patients. It emphasizes improvement of self-management by patients. It involves initial and ongoing teaching and application of empirical therapeutic strategies tailored to the individual patient at a given stage in his or her diabetes. It also involves contacts with patients with the use of modern technologies at various frequencies relevant to the individual patient. It requires application of computer-based methods to analyze key patient data, such as self-monitoring of blood glucose or online glucose sensing values, critically and to provide action prompts to caregivers.

Finally, the prevention of hypoglycemia involves consideration of both the conventional risk factors and those indicative of compromised physiological and behavioral defenses against falling plasma glucose concentrations (Table 8).

Recommendations

3.4 We recommend that both the conventional risk factors and those indicative of compromised defenses against hypoglycemia be considered in a patient with recurrent treatment-induced hypoglycemia (1⊕⊕⊕⊕). The conventional risk factors are excessive or ill-timed dosing of, or wrong type of, insulin or insulin secretagogue, and conditions under which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization is increased, sensitivity to insulin is increased, or insulin clearance is decreased. Compromised defenses against hypoglycemia are indicated by the degree of endogenous insulin deficiency, a history of severe hypoglycemia, hypoglycemia unawareness, or both as well as recent antecedent hypoglycemia, prior exercise or sleep, and lower glycemic goals *per se*.

3.5 With a history of hypoglycemia unawareness (*i.e.* recurrent hypoglycemia without symptoms), we recommend a 2- to 3-wk period of scrupulous avoidance of hypoglycemia, with the anticipation that awareness of hypoglycemia will return in many patients (1⊕⊕◯◯).

3.6 Unless the cause is easily remediable, we recommend that an episode of severe hypoglycemia should lead to a fundamental review of the treatment regimen and the glycemic goals (1⊕⊕⊕⊕).

3.4–3.6 Evidence

The conventional risk factors for hypoglycemia in diabetes (12, 16, 84, 85) are based on the premise that relative or absolute hyperinsulinemia is the sole determinant of risk. They include insulin or insulin secretagogue doses that are excessive, ill-timed, or of the wrong type and conditions in which exogenous glucose delivery or endogenous glucose production is decreased, glucose utilization is increased, sensitivity to insulin is increased, or insulin clearance is decreased (Table 8). However, although each of these needs to be considered carefully, they explain only a minority of episodes of hypoglycemia (168).

Risk factors indicative of HAAF (Table 8) follow directly from the pathophysiology discussed earlier. They include the following: 1) the degree of absolute endogenous insulin deficiency (119, 132, 169–172) that determines the extent to which insulin levels will not decrease and glucagon levels will not increase as plasma glucose levels fall in response to therapeutic hyperinsulinemia; 2) a history of severe hypoglycemia, hypoglycemia unawareness, or both (132, 169, 171), which indicates or implies recent antecedent hypoglycemia that causes an attenuated sympathoadrenal response to subsequent hypoglycemia, the key feature of HAAF. In addition, prior exercise (12, 16, 173) and sleep (12, 16, 174–176) cause HAAF. Long duration of diabetes (110) and classical diabetic autonomic neuropathy (107, 108) are associated with more severe HAAF; 3) aggressive glycemic therapy *per se* as evidenced by lower HbA_{1C} levels, lower glycemic goals, or both (117, 132, 133, 148, 169, 171, 172). As documented in controlled clinical trials (see Refs. 123 and 144), if all other factors are the same, patients treated to lower HbA_{1C} levels are at higher risk for hypoglycemia. That does not, of course, mean that one cannot both improve glycemic control and minimize the risk of hypoglycemia in individual patients (12, 84–86) as discussed earlier. Greater glycemic variation is also associated with an increased risk of hypoglycemia (179).

Parenthetically, whereas there is evidence that glycemic control improves pregnancy outcomes in women with T1DM, this approach is associated with a substantially increased risk of hypoglycemia (180–183). Indeed, the risk factors for HAAF—previous severe hypoglycemia and lower HbA_{1C} levels (180) and previous severe hypoglycemia and impaired awareness of hypoglycemia (182)—are associated with higher rates of severe hypoglycemia in pregnant women with T1DM. Intensive insulin therapy in critically ill patients with or without diabetes also increases the frequency of hypoglycemia (184–186).

When treatment-induced hypoglycemia is a problem, each of the conventional risk factors for hypoglycemia (Table 8) should be considered carefully, and the therapeutic regimen should be adjusted appropriately. Among the sulfonylureas, hypoglycemia is less frequent with glimepiride than with glyburide (glibenclamide) (165, 166). In patients treated with insulin, changes

could include switching from a twice daily NPH and regular or premixed insulin regimen to a basal-bolus insulin regimen. With respect to the latter, use of a long-acting insulin analog as the basal insulin results in less hypoglycemia than NPH insulin (159–161). With a basal-bolus insulin regimen, nocturnal or early morning hypoglycemia implicates the basal insulin whereas daytime hypoglycemia also implicates the prandial insulin. Among the latter, rapid-acting insulin analogs cause less nocturnal hypoglycemia (159). Although an insulin regimen should be tailored to the patient's lifestyle, missed meals do not obviate the need for self-monitoring of blood glucose; that is particularly important at bedtime and, when nocturnal hypoglycemia is a known or suspected problem, during the night. In that instance, continuous glucose monitoring can be helpful. In insulin-treated patients, hypoglycemia often occurs during, or shortly after, exercise (173). Planned exercise should be preceded by carbohydrate ingestion, reduced insulin doses, or both. Unplanned exercise requires careful self-monitoring of blood glucose at a minimum; that will often prompt carbohydrate ingestion. Patients who consume alcohol need to know that alcohol can lower their plasma glucose concentrations. The effects of changes in sensitivity to insulin and of renal failure also need to be considered by the caregiver.

In addition, the risk factors indicative of HAAF in diabetes (Table 8) should be considered. Unless the cause is easily remediable, a history of severe hypoglycemia should prompt consideration of a fundamental adjustment of the regimen. Without that, the risk of a subsequent episode of severe hypoglycemia is high (132). That change could involve use of a different secretagogue or a different insulin regimen as noted earlier, a reduction of secretagogue or insulin doses, and acceptance of higher glycemic goals at least in the short term. Given a history of hypoglycemia unawareness, a 2- to 3-wk period of scrupulous avoidance of hypoglycemia is advisable because that can be expected to restore awareness (102–105). Many patients are prepared to reframe their glycemic goals, particularly once they understand that: 1) the aim is to avoid episodes of hypoglycemia rather than worsening glycemic control and 2) the strategy is designed to last weeks rather than months. However, a minority of those with unawareness have developed major psychological barriers that prevent them from cooperating with such an approach. These individuals, who may have a morbid fear of complications, often take frequent additional insulin to try and prevent their glucose levels from rising above normal. Ultimately, such behavior can prevent a successful outcome, and unawareness continues accompanied by frequent severe hypoglycemia. Finally, a history of late postexercise hypoglycemia, nocturnal hypoglycemia, or both should prompt appropriately timed regimen adjustments (generically less insulin, more carbohydrate ingestion, or both) or, failing these, a pharmacological bedtime treatment (187).

Recommendation

3.7 We recommend that urgent treatment of hypoglycemia should be accomplished by ingestion of carbohydrates, if that is feasible, or by parenteral glucagon or glucose if it is not feasible (1⊕⊕⊕⊕).

3.7 Evidence

Hypoglycemia causes functional brain failure that is corrected after the plasma glucose concentration is raised in the vast majority of instances (6). Profound, prolonged hypoglycemia can cause brain death (6). Clearly, the plasma glucose concentration should be raised to normal levels promptly. Data from a rodent model of extreme hypoglycemia suggest that post-hypoglycemic glucose reperfusion contributes to neuronal death (188). The clinical extrapolation of that finding is unclear, but it may be that posttreatment hyperglycemia should be avoided, at least after an episode of profound, prolonged hypoglycemia (6).

In people with diabetes, most episodes of asymptomatic (detected by self-monitoring of blood glucose or continuous glucose sensing) or mild-to-moderate symptomatic hypoglycemia are effectively self-treated by ingestion of glucose tablets or carbohydrate-containing juice, soft drinks, milk, candy, other snacks, or a meal (12, 189). A commonly recommended dose of glucose in adults is 20 g (177). Clinical improvement should occur in 15–20 min. However, the glycemic response to oral glucose is often transient, usually less than 2 h in insulin-induced hypoglycemia (177). Therefore, ingestion of a more substantial snack or a meal shortly after the plasma glucose is raised is generally advisable. (Thus, our recommendation is based on high-quality evidence because of the large treatment effect, as compared with no treatment, associated with carbohydrate intake; compared with alternative doses of carbohydrate or other foods or treatments, the quality of the evidence is very low.) The effects of these commonly used oral treatments of hypoglycemia have not been investigated systematically in the context of contemporary diabetes treatment. Thus, the dose-response relationship between the source of ingested carbohydrate and the plasma glucose level and the time course of response cannot be stated with confidence. This would be a useful subject for investigation. Patients should be advised to monitor their blood glucose levels serially after self-treating an episode of hypoglycemia to ascertain their individual response to the carbohydrate ingested.

Parenteral treatment is necessary when a hypoglycemic patient is unwilling (because of neuroglycopenia) or unable to take carbohydrate orally. Glucagon, injected sc or im in a dose of 1.0 mg in adults by an associate of the patient, is often used. That can be lifesaving, but it often causes substantial, albeit transient, hyperglycemia (177), and it can cause nausea and even vomiting. Although glucagon can be administered iv by medical personnel, in that setting the standard parenteral therapy is iv glucose. A standard initial glucose dose is 25 g. The glycemic response to iv glucose is, of course, transient. A subsequent glucose infusion is often needed, and food should be provided orally as soon as the patient is able to ingest it safely. The duration of a hypoglycemic episode is a function of its cause. A sulfonylurea overdose can result in prolonged hypoglycemia. Hospitalization for prolonged treatment and observation may be necessary. Octreotide has been used to treat sulfonylurea-induced hypoglycemia (178).

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