Hypoglycemia in adults without diabetes mellitus: Clinical manifestations, causes, and diagnosis

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INTRODUCTION

In individuals without diabetes, hypoglycemia is a clinical syndrome with diverse causes. The diagnosis of a true hypoglycemic disorder requires fulfillment of specific criteria known as Whipple's triad.

Whipple's triad comprises the following:

- Symptoms consistent with hypoglycemia (table 1)
- A low plasma glucose concentration measured by a laboratory assay (not a glucose meter or continuous glucose monitor) when symptoms are present
- Resolution of symptoms after the plasma glucose level is raised

Once the presence of a hypoglycemic disorder is verified, a detailed clinical history often suggests a specific underlying cause and can inform subsequent testing.

This topic will review the clinical manifestations, causes, and diagnostic evaluation of hypoglycemia. The evaluation to determine the etiology of hypoglycemia is reviewed separately. Specific causes of hypoglycemia and their respective treatments are reviewed in detail elsewhere, as is the evaluation of hypoglycemia in patients with diabetes.

- (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology".)
- (See "Insulinoma" and "Hypoglycemia in adults with diabetes mellitus".)

- (See "Factitious hypoglycemia".)
- (See "Nonislet cell tumor hypoglycemia".)
- (See "Insulinoma" and "Hypoglycemia in adults with diabetes mellitus".)

EPIDEMIOLOGY

Hypoglycemia is uncommon in individuals who do not have medication-treated diabetes mellitus [1-3]. In a retrospective review of 37,898 non-diabetes, noncritical care hospital admissions, the estimated frequency of a low glucose level (≤55 mg/dL [3 mmol/L], detected by point-of-care or laboratory testing) was 36 per 10,000 admissions [4]. In these patients, hypoglycemia was associated with a variety of non-diabetes drugs, alcohol, and critical illnesses such as sepsis, chronic malnutrition, or liver, kidney, or heart failure. Most patients had multiple possible reasons for hypoglycemia. Only seven patients had unexplained hypoglycemia, which did not recur during the inpatient admission. Few data exist regarding the frequency of unexplained hypoglycemia in the outpatient setting.

CLINICAL MANIFESTATIONS

Symptoms — The symptoms of hypoglycemia are nonspecific and do not differ between individuals with and without diabetes (table 1).

- **Autonomic versus neuroglycopenic symptoms** – Hypoglycemia can cause autonomic and neuroglycopenic symptoms. In individuals without diabetes, the occurrence of neuroglycopenic symptoms provides clinically compelling evidence of pathologic as opposed to physiologic hypoglycemia.

  In studies of insulin-induced hypoglycemia in healthy volunteers, the following findings were noted [5,6]:

  - Autonomic symptoms included tremor, palpitations, and anxiety/arousal (catecholamine mediated, adrenergic) and sweating, hunger, and paresthesias (acetylcholine mediated, cholinergic).

  - Neuroglycopenic symptoms included dizziness, weakness, drowsiness, and confusion or altered mental status.

  The nature of the hypoglycemic symptoms is often consistent across episodes in an individual, and symptoms may occur in the fasting or postprandial state [7]. Hypoglycemic

disorders historically have been classified on the basis of fasting or postprandial timing. However, this classification may have limited utility, as patients may be uncertain about the timing of symptoms in relation to meals. Further, this classification does not always help identify an underlying etiology, as many causes of hypoglycemia can variably produce fasting or postprandial symptoms. Symptoms may not be recognized by the patient, even when evident to an observer. Many patients cannot describe their episodes in any detail because of associated cognitive dysfunction at the time of symptoms, so clinical history also should be obtained from a close family member or friend whenever possible.

In a case series of patients with insulinoma, approximately 77 percent of patients presented with autonomic symptoms and 96 percent with neuroglycopenic symptoms; ≥80 percent had confusion or abnormal behavior, 50 percent lost consciousness or had amnesia for the event, and 12 to 19 percent had grand mal seizures [8,9]. Evidence of recurrent, unequivocal neuroglycopenic symptoms warrants supervised testing for insulin-mediated causes of hypoglycemia. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Supervised testing'.)

- **Glucose threshold for symptom onset** – The onset of hypoglycemic symptoms normally occurs as glucose levels fall below 55 mg/dL (3 mmol/L), although the specific threshold varies among and within individuals over time. A counterregulatory response (eg, release of glucagon and epinephrine) can be detected at glucose levels approximately 10 mg/dL (0.6 mmol/L) higher, before the onset of hypoglycemic symptoms. However, the glycemic thresholds for these counterregulatory responses may shift to higher glucose concentrations in patients with diabetes who have chronic hyperglycemia and to lower glucose concentrations in patients with repeated episodes of hypoglycemia associated with intensive diabetes therapy [10] or an insulinoma [11]. (See "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus", section on 'Counterregulatory hormones'.)

  Impaired awareness (reduced or absent symptoms) of hypoglycemia may occur in individuals without diabetes, particularly those with recent, antecedent hypoglycemia [11]. In these patients, the typical symptoms may occur at progressively lower glucose levels, or symptoms may be altered or entirely absent. Therefore, patients should be queried about both current and remote hypoglycemic symptoms. (See 'Assessment in asymptomatic individuals' below and "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus", section on 'Hypoglycemia-associated autonomic failure'.)

Signs — Diaphoresis and pallor are common signs of hypoglycemia [12]. Heart rate and systolic blood pressure are generally modestly elevated, whereas diastolic blood pressure falls, leading

to an increase in pulse pressure [13]. Neuroglycopenic manifestations (eg, cognitive impairment, behavioral changes, psychomotor abnormalities) are often observable. Occasionally, transient neurologic deficits occur. Permanent neurologic damage is rare and, should it occur, is more likely in individuals with underlying diabetes and prolonged, severe hypoglycemia.

Laboratory findings — The lower limit of the reference range for a normal fasting plasma glucose level is typically 70 mg/dL (3.9 mmol/L). However, lower values can be encountered in healthy individuals, especially during prolonged fasting when insulin secretion appropriately declines and fatty acids increasingly supplant glucose as the primary fuel source. In this setting, glucose can decrease to approximately 50 mg/dL (2.8 mmol/L) and should not be accompanied by impaired cognitive function. The normal response to prolonged fasting includes an elevation in circulating ketone bodies such as beta-hydroxybutyrate. If insulin secretion does not appropriately decline (eg, due to exogenous insulin administration or insulinoma), the transition to fat as a fuel source is inhibited, beta-hydroxybutyrate levels do not rise, and symptomatic hypoglycemia can occur. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Interpretation of supervised fast results'.)

CAUSES OF HYPOGLYCEMIA

Medications and alcohol

- **Medications** – Drugs are the most common cause of hypoglycemia [12]. In addition to insulin, sulfonylureas, and meglitinides, other medications also may cause hypoglycemia (table 2). In a systematic review of 448 publications describing drug-induced hypoglycemia (excluding alcohol and drugs used to treat diabetes), 164 different drugs were associated with hypoglycemia [14]. However, the evidence supporting most of the associations was very low quality. The drugs most associated with hypoglycemia were quinolones, pentamidine, quinine, beta blockers, angiotensin-converting enzyme inhibitors, and insulin-like growth factor 1 (IGF-1).

  The possible contribution of drugs to hypoglycemia in either ill or seemingly well individuals cannot be overemphasized. A thorough review of a patient's medication history including nonprescription medications is essential. In older patients taking glucose-lowering medications, particularly insulin or sulfonylureas, erratic eating with missed meals is a frequent precipitant of hypoglycemia [15]. Other drugs may induce hypoglycemia in patients with underlying kidney or liver dysfunction [15]. Individuals

taking prescription medications are also at risk for hypoglycemia due to prescribing or dispensing errors.

- **Ethanol** – Ethanol inhibits gluconeogenesis but not glycogenolysis [12,16]. Thus, alcohol-induced hypoglycemia typically follows a several-day alcohol binge with hepatic glycogen depletion due to limited ingestion of food. Ethanol may not be detectable in blood at the time of presentation. Gluconeogenesis becomes the sole source of glucose production during prolonged hypoglycemia, so alcohol also can contribute to hypoglycemia progression in patients with insulin-treated diabetes who are at greater risk for prolonged hypoglycemia. Alcohol ingestion is often a contributing cause of hypoglycemia in the emergency department setting.

Illness and comorbid conditions

- **Critical illness** – Severe hypoglycemia can occur during critical illnesses [12]. In a retrospective study of hypoglycemia in an adult intensive care unit, independent risk factors for developing hypoglycemia included diabetes, septic shock, kidney impairment, mechanical ventilation, severity of illness, and treatment with intensive insulin therapy to achieve tight glycemic targets [17].

  Sepsis is a relatively common cause of hypoglycemia [12,18]. Cytokine-accelerated glucose utilization is usually matched by increased glucose production. Hypoglycemia only develops when glucose production is impaired, which may occur as a consequence of cytokine-induced inhibition of gluconeogenesis when glycogen stores are depleted [19,20].

- **Liver or kidney dysfunction** – Impaired kidney or liver function can lead to hypoglycemia, particularly in the setting of reduced food ingestion or exogenous insulin use. The mechanisms of hypoglycemia in chronic kidney disease include impaired renal gluconeogenesis (resulting in decreased renal contributions to endogenous glucose production) and reduced renal clearance of insulin. Gluconeogenesis is also impaired, usually as a late manifestation, in severe liver disease.

- **Malarial infection** – In tropical countries where malaria is endemic, hypoglycemia can result from malaria, its treatment, or both [12,14]. (See "Malaria: Clinical manifestations and diagnosis in nonpregnant adults and children".)

- **Malnourishment** – Malnutrition can cause hypoglycemia due to substrate limitation of gluconeogenesis and glycogenolysis in the setting of glycogen depletion. Hypoglycemia has been reported in patients with anorexia nervosa [21,22].

- **Cortisol deficiency** – Hypoglycemia can occur in patients with cortisol deficiency (Addison disease) [12,23]. However, it is rarely the sole presenting manifestation of cortisol deficiency and almost uniformly accompanied by other signs and symptoms suggestive of the diagnosis. (See "Clinical manifestations of adrenal insufficiency in adults".)

  Individuals with cortisol deficiency, particularly when due to hypopituitarism, may have concurrent hypothyroidism and/or growth hormone deficiency. Although hypothyroidism or growth hormone deficiency alone rarely causes hypoglycemia, either can contribute to more severe or prolonged episodes when hypoglycemia results from another etiology. Hypothyroidism can contribute to hypoglycemia severity through multiple mechanisms including decreased gluconeogenesis and glycogenolysis [24]. Growth hormone is a key component of the glucose counterregulatory response that defends against hypoglycemia. The role of growth hormone in glucose counterregulation is reviewed in detail separately. (See "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus", section on 'Counterregulatory hormones'.)

  Hypoglycemia is more common in infants and children with primary adrenal insufficiency, patients with secondary adrenal insufficiency caused by isolated corticotropin (ACTH) deficiency, and patients with concurrent adrenal insufficiency and type 1 diabetes. In the setting of type 1 diabetes, exogenous insulin action becomes largely unopposed due to loss of the gluconeogenic effect of cortisol. In addition, individuals with either antecedent hypoglycemia or autonomic neuropathy may have reduced epinephrine secretion and, consequently, diminished glucose counterregulation. (See "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus", section on 'Impairment of behavioral and counterregulatory responses'.)

- **Malignancy** – Hypoglycemia has been observed in a small number of patients with nonislet cell tumors; these are usually large, clinically obvious tumors of mesenchymal or epithelial cell types. Hypoglycemia is most often due to tumor production of an insulin-like growth factor (IGF; eg, incompletely processed IGF-2) [12]. Endogenous production of insulin is appropriately suppressed. The diagnosis, pathophysiology, and treatment of nonislet cell tumor hypoglycemia are reviewed in detail elsewhere. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Insulin level <3 microU/mL' and "Nonislet cell tumor hypoglycemia".)

Endogenous hyperinsulinism — Hyperinsulinemic hypoglycemia occurs when insulin secretion fails to fall appropriately in the setting of hypoglycemia; hypoglycemia results from low rates of glucose production rather than high rates of glucose utilization [25].

Endogenous hyperinsulinism is more likely in an otherwise healthy individual with no clinical clues suggesting other common causes of hypoglycemia. The diagnosis is often unrecognized for years. In adults, hypoglycemia due to endogenous hyperinsulinism can be caused by the following (table 3):

- A beta cell secretagogue, such as a sulfonylurea. (See 'Accidental, surreptitious, or malicious hypoglycemia' below.)
- A beta cell tumor (insulinoma). (See "Insulinoma".)
- A functional beta cell disorder that can occur as a feature of the noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). (See "Noninsulinoma pancreatogenous hypoglycemia syndrome".)
- After gastric bypass or Nissen fundoplication when a mismatch occurs between postprandial glucose disappearance and the offset of insulin action. This mismatch is due to rapid transit of calories through the upper gastrointestinal tract [26,27]. Individuals who have undergone gastric bypass surgery also may have postprandial hyperinsulinemic hypoglycemia.
- Insulin autoimmune hypoglycemia occurs in patients who have antibodies directed to endogenous insulin or to the insulin receptor. Symptoms can occur postprandially, fasting, or in both states. In patients with insulin antibody-mediated hypoglycemia, insulin secreted in response to a meal is thought to bind to antibodies and then disassociate in an unregulated fashion, causing hyperinsulinemia and hypoglycemia. In patients with antibodies to the insulin receptor, hypoglycemia occurs as a result of antibody activation of the receptor [28].
- Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) or congenital hyperinsulinism, while very rare, is the most common cause of persistent hypoglycemia in infants. PHHI is a genetic disorder with both familial and sporadic forms, characterized by dysregulation of insulin secretion. (See "Pathogenesis, clinical presentation, and diagnosis of congenital hyperinsulinism".)

Accidental, surreptitious, or malicious hypoglycemia — The possibility of accidental, surreptitious, or even malicious hypoglycemia should be considered when the cause of pathologic hypoglycemia is not apparent [12]. Accidental hypoglycemia can result from medical, pharmacy, or patient errors, such as the mistaken use of an oral hypoglycemic medication by an older spouse of a patient with diabetes. It may also occur after ingestion of herbal products contaminated with sulfonylureas [29] or after covert self-administration of an oral hypoglycemic

drug or insulin by a patient with or without diabetes. Finally, eating unripe Ackee fruit can result in severe hypoglycemia (Jamaican vomiting illness) mediated by toxins called hypoglycins that inhibit hepatic gluconeogenesis.

Surreptitious use of a glucose-lowering medication, often a sulfonylurea, occurs more commonly in a person who is knowledgeable about the drug and has immediate access to it. Malicious hypoglycemia involves administration of an insulin secretagogue or insulin to another person with the intent to cause hypoglycemia. Synthetic insulin analogs are not detected by some insulin assays, and specialized assays may be needed for their detection [30]. (See "Factitious hypoglycemia".)

DIAGNOSTIC EVALUATION

Whom to evaluate — A full diagnostic evaluation is required for healthy-appearing individuals with a suspected hypoglycemic disorder. In ill or medicated patients, when hypoglycemia is readily attributable to the underlying illness or its treatment (table 3), additional evaluation for an underlying hypoglycemic disorder is often not necessary. However, if uncertainty exists as to whether the comorbid illness or medication is the sole cause of hypoglycemia, then additional evaluation is warranted.

Assessment should begin with review of the patient's history in detail, including the nature and timing of symptoms (particularly in relationship to meals), existence of underlying illnesses or conditions, medications taken by the individual and by family or other household members, and surgical and social history.

Hypoglycemic disorders are uncommon in people without diabetes, so the approach to evaluation is largely based upon clinical experience and is consistent with the 2009 Endocrine Society guidelines for the evaluation and management of hypoglycemic disorders in adults [12].

Criteria for a hypoglycemic disorder — Documentation of Whipple's triad helps to establish the presence of a hypoglycemic disorder [12].

Whipple's triad comprises the following:

- Symptoms consistent with hypoglycemia (table 1)
- A low plasma glucose concentration measured by a laboratory assay (not a glucose meter or continuous glucose monitor) when symptoms are present
- Resolution of symptoms after the plasma glucose level is raised

Only those patients who meet the criteria for Whipple's triad require full evaluation for causes of a hypoglycemic disorder, as the presence of symptoms supports a pathologic significance of the low blood glucose. In patients in whom Whipple's triad has not been documented but strong clinical suspicion exists for a hypoglycemic disorder (eg, based on clinical history and fingerstick blood glucose measurements), then supervised testing can be performed to document the presence of Whipple's triad. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Importance of supervised evaluation'.)

In a person without diabetes, the presence of a hypoglycemic disorder cannot be established solely on the basis of a low glucose concentration [12]. For example, healthy individuals, particularly young women, may have numerically low glucose concentrations after an overnight or prolonged fast without attendant symptoms; these low glucose concentrations reflect normal physiology rather than the presence of a hypoglycemic disorder.

Conversely, patients who have sympathoadrenal symptoms (anxiety, weakness, tremor, perspiration, or palpitations) with normal concurrent glucose concentrations have a low probability of having a hypoglycemic disorder. This presentation is most common in individuals with predominantly postprandial symptoms, and, in such individuals, symptoms often resolve after dietary modification. (See "Evaluation of postprandial symptoms of hypoglycemia in adults without diabetes", section on 'Postprandial syndrome'.)

Assessment in symptomatic individuals

Measure glucose during symptoms — In individuals with symptoms suggestive of hypoglycemia, the first step in the evaluation is to review all available glucose measurements obtained at the time of symptoms (algorithm 1). If no glucose data are available, measure glucose during a symptomatic episode.

Laboratory measurement or home glucose monitoring with fingerstick and glucose meter are both reasonable strategies for evaluating glucose values during symptomatic episodes. Laboratory measurements are preferable when possible; glucose meters are not sufficiently accurate to reliably discriminate between glucose levels in the low-normal and hypoglycemic range. Nonetheless, home glucose monitoring can help stratify patients by the likelihood of an underlying hypoglycemic disorder and thereby determine the need for subsequent evaluation. Data from continuous glucose monitoring devices are not part of the evaluation of hypoglycemia in individuals without diabetes because these devices are less accurate than glucose meters when glucose levels are low. The interpretation of these glucose measurements is discussed below. (See 'Interpretation of glucose levels in symptomatic individuals' below.)

- **Laboratory glucose measurement** – In hospitalized patients, laboratory glucose measurement is the preferred strategy and usually can be coordinated readily upon symptom onset. Ambulatory patients in whom symptomatic episodes follow a predictable pattern can be provided a laboratory requisition for glucose measurement. Patients should report to the laboratory and then try to elicit symptoms (eg, through continued fasting or consumption of a meal that typically provokes symptoms). Once symptoms develop, blood is collected for glucose measurement. Patients should be counseled about the importance of adequately treating hypoglycemia before leaving the laboratory. This strategy often requires prolonged waiting in the laboratory, and some patients may wish to avoid this inconvenience. Strategies to reverse hypoglycemia are discussed elsewhere. (See "Hypoglycemia in adults with diabetes mellitus", section on 'Reversing hypoglycemia'.)

  For patients undergoing laboratory glucose measurement, additional laboratory tests should be measured at the time of the symptomatic hypoglycemia. If hypoglycemia occurs, concurrent measurement of insulin, C-peptide, and proinsulin may provide information about the underlying etiology. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Interpretation of supervised fast results'.)

  Proper collection and processing of blood samples for laboratory measurement are essential to prevent artifactual hypoglycemia. (See 'Exclude artifactual hypoglycemia' below.)

- **Home glucose monitoring** – Ambulatory patients alternatively may be provided a glucose meter for home monitoring. Home blood glucose monitoring can be used to establish both the occurrence of low blood glucose and the temporal relationship between glucose levels and hypoglycemic symptoms. Patients should check their glucose using a fingerstick and glucose meter whenever they experience hypoglycemic symptoms. They should record all glucose values and maintain a log of symptoms experienced at the time of glucose measurement.

  We generally ask patients to monitor their glucose for several weeks and bring a log of their recorded symptoms and glucose measurements to the next clinic visit. However, patients should contact their health care provider **immediately** if they have a glucose measurement <65 mg/dL (3.6 mmol/L) with concurrent hypoglycemic symptoms. We also provide detailed instructions about the treatment of hypoglycemia and counsel patients to remeasure any glucose values <80 mg/dL (4.4 mmol/L). Patients should record whether their symptoms resolve after hypoglycemia reversal to demonstrate the third criterion of

Whipple's triad. (See "Hypoglycemia in adults with diabetes mellitus", section on 'Reversing hypoglycemia'.)

Interpretation of glucose levels in symptomatic individuals — Interpretation of glucose levels depends in part on whether glucose was measured by laboratory assay or glucose meter (algorithm 1).

Laboratory measurement (venipuncture) thresholds

- **Venipuncture glucose <65 mg/dL** – If the venipuncture glucose is <65 mg/dL (3.6 mmol/L) at the time of symptoms, an underlying hypoglycemic disorder is possible. Any patient with a venipuncture glucose <65 mg/dL (3.6 mmol) and concurrent hypoglycemic symptoms should be referred to an endocrinologist for additional evaluation. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology' and "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Supervised testing'.)

- **Venipuncture glucose ≥65 mg/dL** – If the venipuncture glucose is ≥65 mg/dL (3.6 mmol/L) at the time of symptoms, hypoglycemia as a cause of the symptoms is very unlikely [1]. Such patients generally do not require additional evaluation for a hypoglycemic disorder. The differential diagnosis for autonomic symptoms is extensive and includes postprandial syndrome, cardiac disease (arrhythmia, valvular heart disease), medications, and psychiatric (eg, anxiety) and endocrine (hyperthyroidism, pheochromocytoma) disorders. (See "Evaluation of postprandial symptoms of hypoglycemia in adults without diabetes", section on 'Postprandial syndrome' and "Evaluation of palpitations in adults" and "Generalized anxiety disorder in adults: Epidemiology, pathogenesis, clinical manifestations, course, assessment, and diagnosis" and "Overview of the clinical manifestations of hyperthyroidism in adults" and "Clinical presentation and diagnosis of pheochromocytoma".)

Glucose meter thresholds — Although glucose meters are not accurate enough in the low range to unequivocally establish the presence of hypoglycemia or fulfillment of Whipple's triad, glucose meter measurements can inform clinical suspicion for a hypoglycemic disorder and therefore facilitate selection of patients for further evaluation.

- **Fingerstick glucose <65 mg/dL** – If any glucose values are <65 mg/dL (3.6 mmol/L) with associated hypoglycemic symptoms that resolve with reversal of hypoglycemia, the presence of a hypoglycemic disorder is likely. Additional evaluation with laboratory glucose testing is necessary to confirm hypoglycemia and establish an underlying etiology, and evaluation should be completed under the care of an endocrinologist. (See

"Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology' and "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Supervised testing'.)

- **Fingerstick glucose ≥65 to 79 mg/dL** – Glucose values ≥65 to 79 mg/dL (3.6 to 4.4 mmol/L) during symptomatic episodes do not usually represent an underlying hypoglycemic disorder, although the presence of a hypoglycemic disorder cannot be excluded. The patient may continue home glucose monitoring, usually for approximately one to three more months depending on clinical suspicion and frequency of symptomatic episodes. If glucose values remain ≥65 mg/dL (3.6 mmol/L), home glucose monitoring may be discontinued, and no further evaluation is necessary.

- **Fingerstick glucose ≥80 mg/dL** – If a patient has sympathoadrenal symptoms with fingerstick glucose measurements ≥80 mg/dL (4.4 mmol/), a hypoglycemic disorder is excluded as the cause of symptoms. Home glucose monitoring may be discontinued.

Assessment in asymptomatic individuals — Evaluation for hypoglycemia may be prompted by a low glucose value found incidentally on routine laboratory tests in an asymptomatic patient (algorithm 2).

Exclude artifactual hypoglycemia — The first step in evaluation is to repeat the glucose measurement with proper sample collection and processing to exclude artifactual hypoglycemia. For optimal glucose measurement, whole blood should be collected into a tube containing citrate or sodium fluoride. The sample should be placed on ice and promptly centrifuged.

Artifactual hypoglycemia can occur if an antiglycolytic agent (eg, fluoride) is not present in the blood collection tube and sample processing is delayed. Artifactual hypoglycemia always should be considered in samples from patients with leukocytosis, severe hemolysis, or erythrocytosis; in such samples, the abundant leukocytes, nucleated red blood cells, or erythrocytes consume glucose after blood collection, leading to a misleadingly low glucose concentration [31-34].

Subsequent evaluation depends on the severity of the low glucose value.

Interpretation of glucose levels in asymptomatic individuals

- **Venipuncture glucose <40 mg/dL** – For any patient with a documented glucose measurement <40 mg/dL (2.2 mmol/L), suspicion for an underlying hypoglycemic disorder is sufficiently high to warrant additional evaluation even in the absence of concurrent symptoms. In some individuals, the absence of symptoms reflects impaired awareness of

hypoglycemia; recurrent hypoglycemia can cause an attenuated counterregulatory response with blunted or absent sympathoadrenal symptoms. Thus, a blunted or absent symptom response can reflect recent, repeated episodes of hypoglycemia. Further, neuroglycopenic symptoms are often underrecognized by patients. Therefore, the next steps should include confirmation of hypoglycemia in a supervised setting and, if indicated, additional testing to evaluate the underlying cause. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology' and "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Supervised testing'.)

- **Venipuncture glucose ≥40 to 64 mg/dL** – For individuals with documented glucose values ≥40 to 64 mg/dL (2.2 to 3.6 mmol/L), the next step depends on the clinical context.

  - **Young, healthy individuals** – In a young (aged <40 years), healthy patient, glucose values ≥40 to 64 mg/dL (2.2 to 3.6 mmol/L) without concurrent hypoglycemic symptoms most likely reflect normal physiology, and such patients usually do not require further evaluation. Healthy individuals, particularly young women, may have plasma glucose concentrations between 40 to 60 mg/dL (2.2 to 3.3 mmol) after prolonged fasting.

    If the individual is anxious or uncertainty persists regarding the possibility of a hypoglycemic disorder, home blood glucose monitoring is a reasonable strategy for further assessment. (See 'Assessment in symptomatic individuals' above.)

  - **Adults aged ≥40 years or those who have lost a symptomatic response to hypoglycemia** – In patients aged ≥40 years or those with a history of hypoglycemic symptoms that extinguish over time (ie, individuals who previously experienced hypoglycemic symptoms but no longer experience any symptoms when glucose is low), a glucose of ≥40 to 64 mg/dL (2.2 to 3.6 mmol/L) is concerning for an underlying hypoglycemic disorder. Therefore, in these individuals, a glucose level in this range warrants additional evaluation to determine the etiology of the hypoglycemia. This evaluation should be performed under the care of an endocrinologist. (See "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology'.)

    With increasing age, a low glucose level is less likely to reflect normal physiology. Further, older patients (eg, aged ≥65 years) are more likely to have blunted or absent hypoglycemic symptoms and a higher risk of morbidity during hypoglycemia. Patients who report the loss of a symptomatic response over time should always undergo

additional evaluation, as this history could reflect the evolution of impaired awareness of hypoglycemia that occurs with recurrent hypoglycemic episodes. (See "Physiologic response to hypoglycemia in healthy individuals and patients with diabetes mellitus", section on 'Hypoglycemia-associated autonomic failure'.)

- **Venipuncture glucose ≥65 mg/dL** – For individuals with a glucose value ≥65 mg/dL (3.6 mmol/L), an underlying hypoglycemic disorder is unlikely. In such patients, no additional evaluation is generally required.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hypoglycemia in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Low blood sugar in people with diabetes (The Basics)" and "Patient education: Low blood sugar in people without diabetes (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Hypoglycemia is uncommon in individuals who do not have medication-treated diabetes mellitus. (See 'Epidemiology' above.)

- **Symptoms** – The symptoms of hypoglycemia are nonspecific and may include tremor, palpitations, sweating, hunger, paresthesias, cognitive impairment, behavioral changes, and psychomotor abnormalities (table 1). (See 'Clinical manifestations' above.)

- **Causes** – In patients with comorbid conditions, medications, critical illness, and liver or kidney dysfunction are common causes of hypoglycemia, whereas in healthy individuals, the most common causes of hypoglycemia are endogenous hyperinsulinism and factitious hypoglycemia (table 2 and table 3). (See 'Causes of hypoglycemia' above.)

- **Diagnostic evaluation**

  - **Whom to evaluate** – A full diagnostic evaluation is required for healthy-appearing individuals with a suspected hypoglycemic disorder. In ill or medicated patients, when hypoglycemia is readily attributable to the underlying illness or its treatment (table 2 and table 3), additional evaluation for an underlying hypoglycemic disorder is often not necessary. However, if uncertainty exists as to whether the comorbid illness or medication is the sole cause of hypoglycemia, then additional evaluation is warranted.

  - **Criteria for a hypoglycemic disorder** – The diagnosis of a hypoglycemic disorder in individuals without diabetes is based upon fulfillment of the three criteria of Whipple's triad (see 'Criteria for a hypoglycemic disorder' above):

    - Symptoms consistent with hypoglycemia
    - A low plasma glucose concentration (measured by laboratory assay) at the time of symptoms
    - Resolution of symptoms after the plasma glucose concentration is raised

  - **Initial assessment**

    - **Symptomatic individuals** – In patients who present with hypoglycemic symptoms, glucose measurement during a symptomatic episode is the first step in evaluation (algorithm 1). Laboratory measurement or home glucose monitoring with fingerstick and glucose meter are both reasonable strategies for obtaining glucose values during symptomatic episodes. Individuals with a glucose level <65 mg/dL (3.6 mmol/L) during symptoms should undergo further evaluation under the care of an endocrinologist. (See 'Assessment in symptomatic individuals' above and "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology'.)

- **Asymptomatic individuals** – Evaluation for hypoglycemia may be prompted by a low glucose value found incidentally on routine laboratory tests in an asymptomatic patient (algorithm 2). In such cases, artifactual hypoglycemia must be excluded. Patients with a verified plasma glucose <40 mg/dL (2.2 mmol/L) always require additional evaluation under the care of an endocrinologist. For patients with glucose levels ≥40 to 64 mg/dL (2.2 to 3.6 mmol/L), subsequent evaluation depends on the patient's age, clinical history, and overall health status. (See 'Assessment in asymptomatic individuals' above and "Hypoglycemia in adults without diabetes mellitus: Determining the etiology", section on 'Initial assessment to determine the etiology'.)

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REFERENCES

1. Service FJ. Hypoglycemic disorders. N Engl J Med 1995; 332:1144.
2. Service FJ. Classification of hypoglycemic disorders. Endocrinol Metab Clin North Am 1999; 28:501.
3. Sako A, Yasunaga H, Matsui H, et al. Hospitalization with hypoglycemia in patients without diabetes mellitus: A retrospective study using a national inpatient database in Japan, 2008-2012. Medicine (Baltimore) 2017; 96:e7271.
4. Nirantharakumar K, Marshall T, Hodson J, et al. Hypoglycemia in non-diabetic in-patients: clinical or criminal? PLoS One 2012; 7:e40384.
5. Hepburn DA, Deary IJ, Frier BM, et al. Symptoms of acute insulin-induced hypoglycemia in humans with and without IDDM. Factor-analysis approach. Diabetes Care 1991; 14:949.
6. Towler DA, Havlin CE, Craft S, Cryer P. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993; 42:1791.

7. Placzkowski KA, Vella A, Thompson GB, et al. Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987-2007. J Clin Endocrinol Metab 2009; 94:1069.
8. Peltola E, Hannula P, Huhtala H, et al. Characteristics and Outcomes of 79 Patients with an Insulinoma: A Nationwide Retrospective Study in Finland. Int J Endocrinol 2018; 2018:2059481.
9. Service FJ. Insulinoma. In: Hypoglycemic Disorders: Pathogenesis, Diagnosis, and Treatmen t, Service FJ (Ed), GK Hall, Boston 1983. p.111.
10. Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. Diabetes 1988; 37:901.
11. Mitrakou A, Fanelli C, Veneman T, et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med 1993; 329:834.
12. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:709.
13. Fisher BM, Gillen G, Hepburn DA, et al. Cardiac responses to acute insulin-induced hypoglycemia in humans. Am J Physiol 1990; 258:H1775.
14. Murad MH, Coto-Yglesias F, Wang AT, et al. Clinical review: Drug-induced hypoglycemia: a systematic review. J Clin Endocrinol Metab 2009; 94:741.
15. Parekh TM, Raji M, Lin YL, et al. Hypoglycemia after antimicrobial drug prescription for older patients using sulfonylureas. JAMA Intern Med 2014; 174:1605.
16. Marks V, Teale JD. Drug-induced hypoglycemia. Endocrinol Metab Clin North Am 1999; 28:555.
17. Krinsley JS, Grover A. Severe hypoglycemia in critically ill patients: risk factors and outcomes. Crit Care Med 2007; 35:2262.
18. Miller SI, Wallace RJ Jr, Musher DM, et al. Hypoglycemia as a manifestation of sepsis. Am J Med 1980; 68:649.
19. Maitra SR, Wojnar MM, Lang CH. Alterations in tissue glucose uptake during the hyperglycemic and hypoglycemic phases of sepsis. Shock 2000; 13:379.
20. Metzger S, Nusair S, Planer D, et al. Inhibition of hepatic gluconeogenesis and enhanced glucose uptake contribute to the development of hypoglycemia in mice bearing interleukin-1beta- secreting tumor. Endocrinology 2004; 145:5150.
21. Mehler PS, Blalock DV, Walden K, et al. Medical findings in 1,026 consecutive adult inpatient-residential eating disordered patients. Int J Eat Disord 2018; 51:305.

22. Rylander M, Brinton JT, Sabel AL, et al. A comparison of the metabolic complications and hospital course of severe anorexia nervosa by binge-purge and restricting subtypes. Eat Disord 2017; 25:345.
23. Yamamoto T, Fukuyama J, Hasegawa K, Sugiura M. Isolated corticotropin deficiency in adults. Report of 10 cases and review of literature. Arch Intern Med 1992; 152:1705.
24. Eom YS, Wilson JR, Bernet VJ. Links between Thyroid Disorders and Glucose Homeostasis. Diabetes Metab J 2022; 46:239.
25. Rizza RA, Haymond MW, Verdonk CA, et al. Pathogenesis of hypoglycemia in insulinoma patients: suppression of hepatic glucose production by insulin. Diabetes 1981; 30:377.
26. Salehi M, Vella A, McLaughlin T, Patti ME. Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies. J Clin Endocrinol Metab 2018; 103:2815.
27. Butler PC, Caumo A, Zerman A, et al. Methods for assessment of the rate of onset and offset of insulin action during nonsteady state in humans. Am J Physiol 1993; 264:E548.
28. Lupsa BC, Chong AY, Cochran EK, et al. Autoimmune forms of hypoglycemia. Medicine (Baltimore) 2009; 88:141.
29. Kao SL, Chan CL, Tan B, et al. An unusual outbreak of hypoglycemia. N Engl J Med 2009; 360:734.
30. Egan AM, Galior KD, Maus AD, et al. Pitfalls in Diagnosing Hypoglycemia Due to Exogenous Insulin: Validation and Utility of an Insulin Analog Assay. Mayo Clin Proc 2022; 97:1994.
31. Gambino R, Piscitelli J, Ackattupathil TA, et al. Acidification of blood is superior to sodium fluoride alone as an inhibitor of glycolysis. Clin Chem 2009; 55:1019.
32. Goodenow TJ, Malarkey WB. Leukocytosis and artifactual hypoglycemia. JAMA 1977; 237:1961.
33. Macaron CI, Kadri A, Macaron Z. Nucleated red blood cells and artifactual hypoglycemia. Diabetes Care 1981; 4:113.
34. Theofilogiannakos EK, Giannakoulas G, Ziakas A, et al. Pseudohypoglycemia in a patient with the Eisenmenger syndrome. Ann Intern Med 2010; 152:407.

Topic 1763 Version 27.0

GRAPHICS

Rapid overview for hypoglycemia in adults, other than significant sulfonylurea overdose

Clinical features

- **Any** patient with acute change in mental status or coma should undergo rapid assessment of blood glucose as a possible cause.
- All findings of hypoglycemia are nonspecific, including the following:
  - Autonomic response (tends to occur with blood glucose below 65 mg/dL)
    - Sweating
    - Weakness
    - Tachycardia
    - Palpitations
    - Tremor
    - Nervousness
    - Hunger
    - Paresthesias
  - Neuroglycopenia
    - Irritability
    - Confusion
    - Uncharacteristic behavior
    - Seizure
    - Occasionally, transient focal neurologic deficits
    - Loss of consciousness
    - Visual disturbance

Diagnostic evaluation

- **Obtain blood glucose** concentration as soon as possible (usually with a meter and strips, if available):
  - For symptomatic patient known to have diabetes and with a low glucose value (<70 mg/dL [3.89 mmol/L]), administer treatment. If a glucose test cannot be performed, do not delay. Treat **as if** hypoglycemia has been confirmed.
  - If the glucose is low (<55 mg/dL) and the patient does not have diabetes, draw blood for glucose insulin, C-peptide, and an oral hypoglycemic agent screen, and then treat.
- **Do not delay** treatment if symptomatic hypoglycemia is suspected but rapid blood glucose measurement is not available or blood for diagnostic studies cannot be collected.

Treatment

- If the patient is conscious and able to drink and swallow safely (ie, alert enough to do so and with gag reflex intact), administer a rapidly absorbed carbohydrate (eg, 3 to 4 glucose tablets or a tube of gel with 15 grams, 4 to 6 oz fruit juice or non-diet soda, or a teaspoon of honey or table sugar).*
- If the patient has altered mental status, is unable to swallow, or does not respond to oral glucose administration within 15 minutes, give an IV bolus of 12.5 to 25 g of glucose (25 to 50 mL of 50% dextrose).
- Measure a blood glucose 10 to 15 minutes after the IV bolus. Re-administer 12.5 to 25 grams of glucose as needed to maintain the blood glucose above 80 mg/dL.
- If glucose cannot be given by parenteral or oral routes, give glucagon 1 mg IM or subcutaneously. Response may be transient and should be followed by careful glucose monitoring and oral or IV glucose administration.
- Give additional maintenance glucose by mouth or IV. IV dextrose infusion should ensure delivery of to 9 mg/kg per minute of glucose. Amounts needed vary depending upon the cause and severity of the symptomatic hypoglycemia. Once the patient is able to ingest carbohydrate safely, providing a mixed meal (including carbohydrates, such as a sandwich) is the preferred means of maintaining glucose levels.
- Measure a blood glucose 10 to 15 minutes after the initial IV bolus and monitor every 30 to 60 minutes thereafter until stable (minimum of 4 hours). The measurement method should provide rapid turnaround, preferably at the point of care.
- Admit patients with ingestion of a long-acting hypoglycemic agent, recurrent hypoglycemia during observation, and those unable to eat.

IM: intramuscular; IV: intravenous.

* Patients taking an alpha-glucosidase inhibitor (eg, acarbose, miglitol, voglibose) with symptomatic hypoglycemia should only receive pure glucose (dextrose) orally because digestion and absorption of other carbohydrates (eg, table sugar [sucrose]) will be delayed by these medications and will be less effective in raising blood glucose levels.

Graphic 73797 Version 6.0

Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia

Moderate quality of evidence
Cibenzoline
Gatifloxacin
Pentamidine
Quinine
Indomethacin
Glucagon (during endoscopy)
Low quality of evidence
Chloroquineoxaline sulfonamide
Artesunate/artemisin/artemether
IGF-1
Lithium
Propoxyphene/dextropropoxyphene
Very low quality of evidence
Drugs with >25 cases of hypoglycemia identified
Angiotensin-converting enzyme inhibitors
Angiotensin receptor antagonists
Beta-adrenergic receptor antagonists
Levofloxacin
Mifepristone
Disopyramide
Trimethoprim-sulfamethoxazole
Heparin
6-mercaptopurine

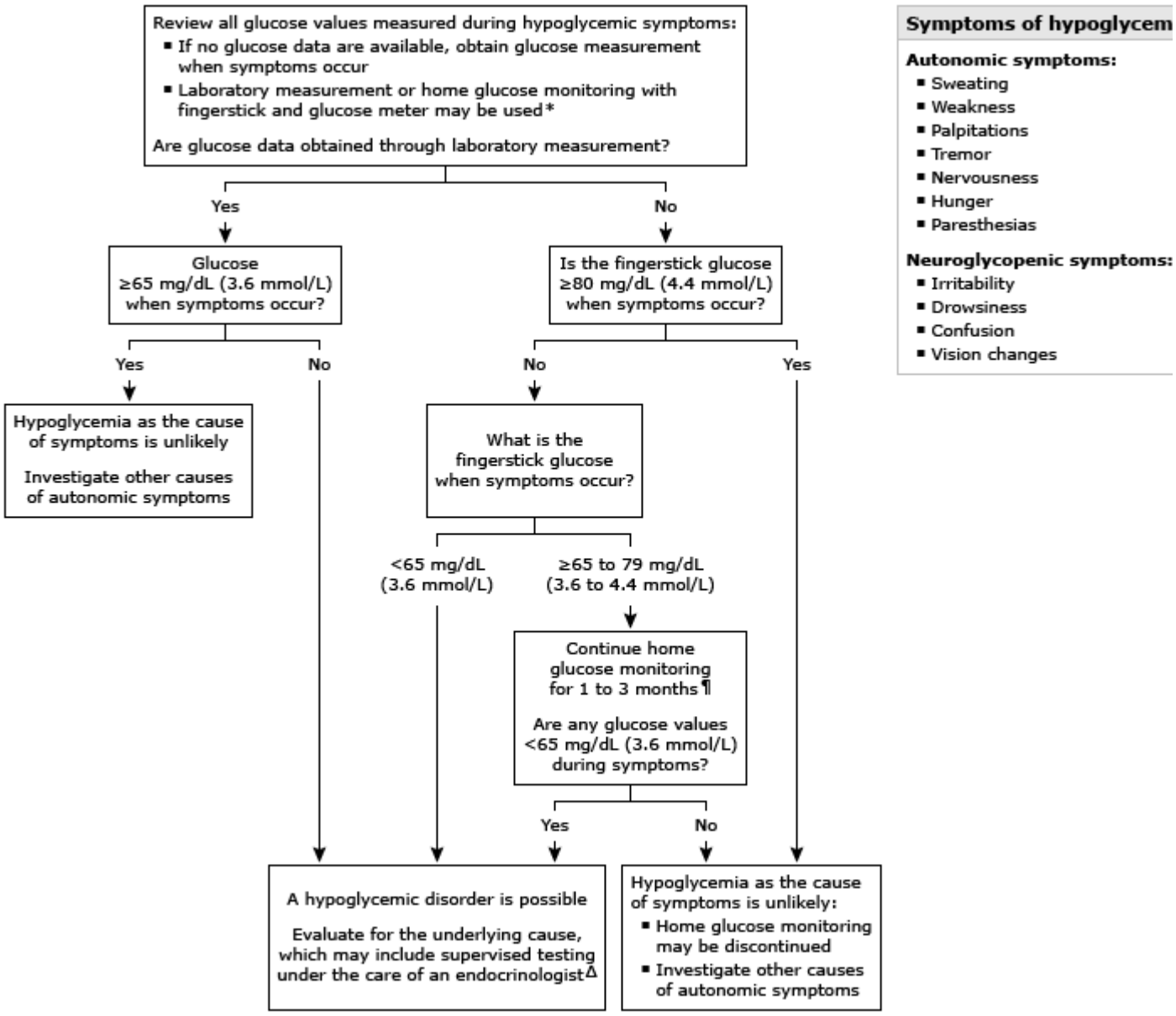
IGF-1: insulin-like growth factor-1.

Graphic 52892 Version 10.0

Causes of hypoglycemia in adults

Ill or medicated individual
1. Drugs
Insulin or insulin secretagogue
Alcohol
Others (refer to UpToDate table on drugs that cause hypoglycemia)
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 beta 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

Evaluation of hypoglycemic symptoms in adults without diabetes mellitus



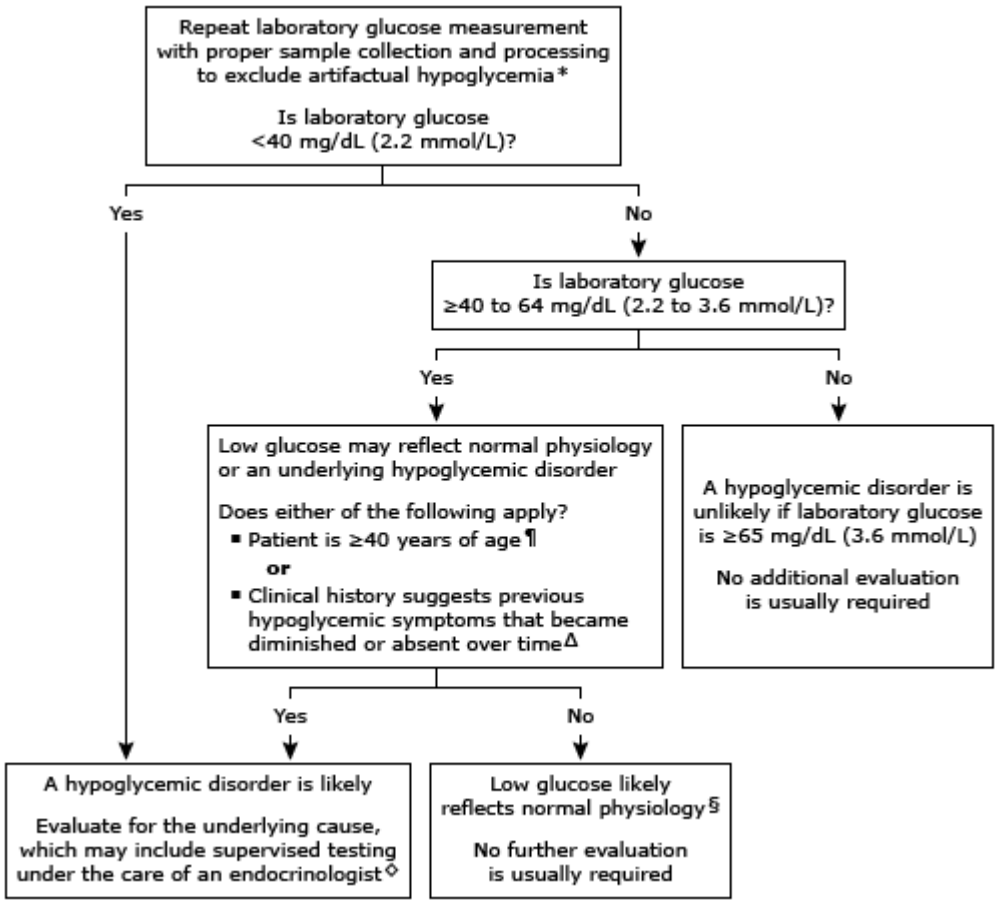
* If laboratory glucose measurement is pursued, insulin, C-peptide, and proinsulin levels should be obtained concurrently at the time of hypoglycemic symptoms. A detailed approach to home blood glucose monitoring with fingersticks and a glucose meter is described in other UpToDate content. Continuous glucose monitoring should **not** be used in the evaluation of hypoglycemic symptoms in individuals without diabetes.

¶ The duration of continued monitoring depends on factors including frequency of hypoglycemic symptoms and clinical suspicion for an underlying hypoglycemic disorder.

Δ Supervised testing can entail a supervised fast or mixed meal test, or evaluation may be performed during a spontaneous episode of hypoglycemia. Selection of a supervised test when hypoglycemia is not fortuitously observed depends on the timing of symptoms in relation to meals. These options are reviewed in detail in other UpToDate content.

Graphic 141449 Version 1.0

Evaluation of hypoglycemia in asymptomatic adults without diabetes mellitus



* Artifactual hypoglycemia can occur if an antiglycolytic agent (eg, fluoride) is not present in the blood collection tube and sample processing is delayed. Artifactual hypoglycemia also may be seen in individuals with leukocytosis, erythrocytosis, or hemolysis.

¶ A low glucose value is less likely to reflect normal physiology in individuals aged ≥40 years and usually warrants further evaluation.

Δ Individuals who report the loss of a symptomatic response to hypoglycemia over time should undergo additional evaluation as this history could reflect the evolution of impaired awareness of hypoglycemia that can occur with recurrent episodes of hypoglycemia.

◇ Supervised testing can entail a supervised fast or mixed meal test, or evaluation may be performed during a spontaneous episode of hypoglycemia. Selection of a supervised test when hypoglycemia is not fortuitously observed depends on the timing of symptoms in relation to meals. These options are reviewed in detail in other UpToDate content.

§ In young (aged <40 years), healthy individuals, glucose values ≥40 to 64 mg/dL (2.2 to 3.6 mmol/L) can reflect normal physiology in the fasting state.

Graphic 141450 Version 1.0