Hypoglycemia

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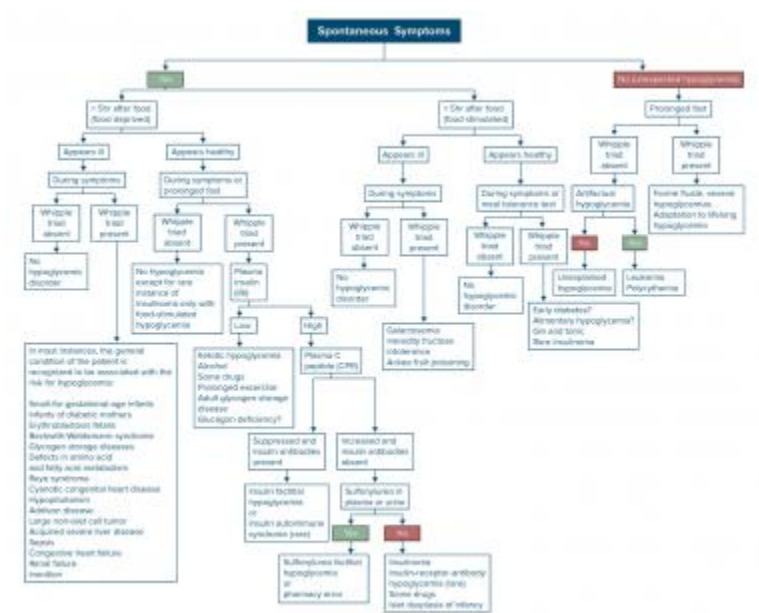
OVERVIEW

Practice Essentials

Hypoglycemia is characterized by a reduction in plasma glucose concentration to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation. This condition typically arises from abnormalities in the mechanisms involved in glucose homeostasis. The most common cause of hypoglycemia in patients with diabetes is injecting a shot of insulin and skipping a meal or overdosing insulin.

The image below depicts a diagnostic algorithm for hypoglycemia.



Diagnostic algorithm. A systematic approach is often required to establish the true cause of hypoglycemia, using an algorithmic approach.

Signs and symptoms

The glucose level at which an individual becomes symptomatic is highly variable (threshold generally at < 50 mg/dL). Carefully review the patient's medication and drug history for potential causes of hypoglycemia (eg, new medications, insulin usage or ingestion of an oral hypoglycemic agent, possible toxic ingestion).

The patient’s medical and/or social history may reveal the following:

- Diabetes mellitus, renal insufficiency/failure, alcoholism, hepatic cirrhosis/failure, other endocrine diseases, or recent surgery
- Central nervous system: Headache, confusion, personality changes
- Ethanol intake and nutritional deficiency
- Weight reduction, nausea and vomiting
- Fatigue, somnolence

Neurogenic or neuroglycopenic symptoms of hypoglycemia may be categorized as follows:

- Neurogenic (adrenergic) (sympathoadrenal activation) symptoms: Sweating, shakiness, tachycardia, anxiety, and a sensation of hunger
- Neuroglycopenic symptoms: Weakness, tiredness, or dizziness; inappropriate behavior (sometimes mistaken for inebriation), difficulty with concentration; confusion; blurred vision; and, in extreme cases, coma and death

Reactive hypoglycemic include the following features:

- More common in overweight and obese people who are insulin-resistant
- May be a frequent precursor to type 2 diabetes
- Possible higher risk in patients with a family history of type 2 diabetes or insulin-resistance syndrome

True loss of consciousness is highly suggestive of an etiology other than reactive hypoglycemia.

Gestational hypoglycemia may have the following features [1] :

- More frequent in women younger than 25 years

- More frequent in women with a preexisting medical condition
- Less frequent in women whose prepregnancy body mass index was ≥30 kg/m^2
- Greater risk of preeclampsia/eclampsia in affected women

See Clinical Presentation for more detail.

Diagnosis

Rapid diagnosis and treatment is essential in any patient with suspected hypoglycemia, regardless of the cause. The Whipple triad is characteristically present: documentation of low blood sugar, presence of symptoms, and reversal of these symptoms when the blood glucose level is restored to normal.

Physical findings, however, are nonspecific in hypoglycemia and are generally related to the central and autonomic nervous systems. Examination includes the following:

- Vital signs
- Head, eyes, ears, nose, and throat
- Cardiovascular
- Neurologic
- Pulmonary
- Gastrointestinal
- Dermatologic

Elderly persons exhibit fewer symptoms of hypoglycemia, and their threshold of plasma glucose is lower at presentation than in younger persons.

Laboratory studies

Patients with no previous history of hypoglycemia require a complete workup to find a potentially treatable disease. Laboratory studies that should be obtained include the following:

- Glucose and electrolyte levels (including calcium, magnesium)
- Oral glucose tolerance test and/or 72-hour fasting plasma glucose
- Complete blood count

Other tests that may be helpful including the following:

- Blood cultures
- Urinalysis
- Serum insulin, cortisol levels, and thyroid hormone levels
- C-peptide levels
- Proinsulin

Imaging studies

Imaging modalities to evaluate insulinomas may include the following:

- CT scanning
- MRI
- Octreotide scanning

Procedures

Selective percutaneous transhepatic venous sampling may be performed to localize an insulinoma to the pancreatic head, body, or tail. Selective arteriography is also often helpful in localizing insulin-secreting lesions.

See Workup for more detail.

Management

Pharmacotherapy

The mainstay of therapy for hypoglycemia is glucose. Other medications may be administered based on the underlying cause or the accompanying symptoms.

Medications used in the treatment of hypoglycemia include the following:

- Glucose supplements (eg, dextrose)
- Glucose-elevating agents (eg, glucagon)
- Inhibitors of insulin secretion (eg, diazoxide, octreotide)
- Antineoplastic agents (eg, streptozocin)

Other therapies

- Fasting hypoglycemia: Dietary therapy (frequent meals/snacks preferred, especially at night, with complex carbohydrates); IV

glucose infusion; IV octreotide

- Reactive hypoglycemia: Dietary therapy (restriction of refined carbohydrates, avoidance of simple sugars, increased meal frequency, increased protein and fiber); alpha-glucosidase inhibitors

Surgery

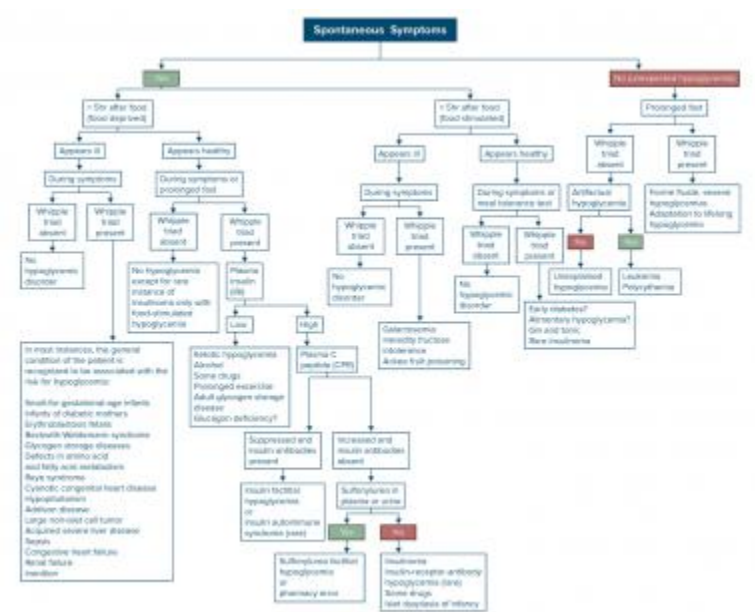
Definitive treatment for fasting hypoglycemia caused by a tumor is surgical resection. The success rate is good for benign islet-cell adenomas, and the success rate for malignant islet-cell tumors can be as high as 50%.

See Treatment and Medication for more detail.

Background

Hypoglycemia is a clinical situation characterized by a reduction in plasma glucose concentration to a level that may induce symptoms or signs such as altered mental status and/or sympathetic nervous system stimulation. The glucose level at which an individual becomes symptomatic is highly variable, although a plasma glucose level less than 50 mg/dL is generally considered the threshold. Hypoglycemia typically arises from abnormalities in the mechanisms involved in glucose homeostasis.

To diagnose hypoglycemia, the Whipple triad is characteristically present. This triad includes the documentation of low blood sugar, presence of symptoms, and reversal of these symptoms when the blood sugar level is restored to normal. See a diagnostic algorithm for hypoglycemia, below.



Diagnostic algorithm. A systematic approach is often required to establish the true cause of hypoglycemia, using an algorithmic approach.

See also Pediatric Hypoglycemia, Neonatal Hypoglycemia, Emergent Management of Acute Symptoms of Hypoglycemia, and Congenital Hyperinsulinism.

Pathophysiology

Hypoglycemic symptoms are related to sympathetic activation and brain dysfunction secondary to decreased levels of glucose. Stimulation of the sympathoadrenal nervous system leads to sweating, palpitations, tremulousness, anxiety, and hunger. Reduction in cerebral glucose availability (ie, neuroglycopenia) can manifest as confusion, difficulty with concentration, irritability, hallucinations, focal impairments (eg, hemiplegia), and, eventually, coma and death.

The adrenergic symptoms often precede the neuroglycopenic symptoms and, thus, provide an early warning system for the patient. Studies have shown that the primary stimulus for the release of catecholamines is the absolute level of plasma glucose; the rate of decrease of glucose is less important. Previous blood sugar levels can influence an individual's response to a particular level of blood sugar. However, it is important to note that a patient with repeated hypoglycemia can have almost no symptoms (hypoglycemic unawareness). The threshold at which a patient feels the hypoglycemic symptoms decreases with repeated episodes of hypoglycemia.

Etiology

Causes of hypoglycemia are varied, but it is seen most often in diabetic patients. Hypoglycemia may result from medication changes or overdoses, infection, diet changes, metabolic changes over time, or activity changes; however, no acute cause may be found. Other causes include alimentary problems, idiopathic causes, fasting, insulinoma, endocrine problems, extrapancreatic causes, hepatic disease, post bariatric surgery, and miscellaneous causes.

Fasting hypoglycemia

Nesidioblastosis is a rare cause of fasting hypoglycemia in infants and an extremely rare cause in adults. This condition is characterized by a diffuse budding of insulin-secreting cells from pancreatic duct epithelium and pancreatic microadenomas of such cells.

Causes of fasting hypoglycemia usually diagnosed in infancy or childhood include inherited liver enzyme deficiencies that restrict hepatic glucose release (deficiencies of glucose-6-phosphatase, fructose-1,6-

diphosphatase, phosphorylase, pyruvate carboxylase, phosphoenolpyruvate carboxykinase, or glycogen synthetase).

Inherited defects in fatty acid oxidation, including that resulting from systemic carnitine deficiency and inherited defects in ketogenesis (3-hydroxy-3-methylglutaryl-CoA lyase deficiency) cause fasting hypoglycemia by restricting the extent to which nonneural tissues can derive their energy from plasma free fatty acids (FFA) and ketones during fasting or exercise. This results in an abnormally high rate of glucose uptake by nonneural tissues under these conditions.

Several cases of nesidioblastosis were reported recently after gastric bypass surgery.

Drugs

Ethanol (including propranolol plus ethanol), haloperidol, pentamidine, quinine, salicylates, and sulfonamides ("sulfa drugs") have been associated with hypoglycemia. Other drugs that may be related to this condition include oral hypoglycemics, phenylbutazone, insulin, bishydroxycoumarin, p-aminobenzoic acid, propoxyphene, stanozolol, hypoglycin, carbamate insecticide, disopyramide, isoniazid, methanol, methotrexate, tricyclic antidepressants, cytotoxic agents, organophosphates, didanosine, chlorpromazine, fluoxetine, sertraline, fenfluramine, trimethoprim, 6-mercaptopurine, thiazide diuretics, thioglycolate, tremetol, ritodrine, disodium ethylenediaminetetraacetic acid (EDTA), clofibrate, angiotensin converting enzyme (ACE) inhibitors, and lithium.

A study by Fournier and colleagues indicates that treatment for pain with the opioid analgesic tramadol increases a patient’s risk of being hospitalized for hypoglycemia. Information from the United Kingdom Clinical Practice Research Datalink and the Hospital Episode Statistics database was analyzed for 28,110 patients who were newly prescribed tramadol and 305,924 individuals who were newly prescribed codeine, all for noncancer pain, with 11,019 controls also included in the study. Using case-control, cohort, and case-crossover analysis, the investigators found that tramadol increased the risk of hospitalization for hypoglycemia by more than three-fold, with the risk particularly elevated in the first 30 days of treatment. The actual risk was small, however, occurring in about 7 patients per 10,000 annually. [2, 3]

A study by Eriksson et al indicated that in patients with type 2 diabetes undergoing second-line treatment, the combination of metformin and sulfonylurea carries a greater risk for severe hypoglycemia, cardiovascular disease, and all-cause mortality than does the combination of metformin and dipeptidyl peptidase-4 inhibitor (DPP4i). [4]

Similarly, a study by Gautier et al found that patients with type 2 diabetes

treated with metformin plus insulin secretagogues (such as sulfonylurea or glinide) were more likely to experience hypoglycemia than were those treated with metformin plus DPP4i while starting insulin. Both groups achieved similar glycemic control. [5]

Surreptitious sulfonylurea use/abuse

Factitious hypoglycemia or self-induced hypoglycemia can be seen in healthcare workers or in relatives who care for diabetic family members at home. (see Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus for further discussion, including the diagnostic use of C-peptide levels and hemoglobin A1C).

Exogenous insulin

Surreptitious use of insulin may be seen, typically among those likely to have access to insulin. Measurement of insulin level along with C-peptide is very crucial in making this diagnosis.

Endogenous insulin or insulin-receptor–mediated hypoglycemia

Sources of endogenous insulin include insulin-producing tumors of pancreas and non–beta-cell tumors.

Insulin-producing tumors of pancreas

Islet cell adenoma or carcinoma (insulinoma) is an uncommon and usually curable cause of fasting hypoglycemia and is most often diagnosed in adults. It may occur as an isolated abnormality or as a component of the multiple endocrine neoplasia type I (MEN I) syndrome.

Carcinomas account for only 10% of insulin-secreting islet cell tumors. Hypoglycemia in patients with islet cell adenomas results from uncontrolled insulin secretion, which may be clinically determined during fasting and exercise. Approximately 60% of patients with insulinoma are female. Insulinomas are uncommon in persons younger than 20 years and are rare in those younger than 5 years. The median age at diagnosis is about 50 years, except in patients with MEN syndrome, in which the median age is in the mid third decade of life. Ten percent of patients with insulinoma are older than 70 years.

Non–beta-cell tumors

Hypoglycemia may also be caused by large non–insulin-secreting tumors, most commonly retroperitoneal or mediastinal malignant mesenchymal tumors. The tumor secretes abnormal insulinlike growth factor (large IGF-II), which does not bind to its plasma binding proteins. This increase in

free IGF-II exerts hypoglycemia through the IGF-I or the insulin receptors. The hypoglycemia is corrected when the tumor is completely or partially removed and usually recurs when the tumor regrows.

Reactive hypoglycemia

Reactive hypoglycemia can be idiopathic, due to alimentary problems, or a result of congenital enzyme deficiencies.

Alimentary hypoglycemia is another form of reactive hypoglycemia that occurs in patients who have had previous upper gastrointestinal (GI) surgical procedures (gastrectomy, gastrojejunostomy, vagotomy, pyloroplasty) and allows rapid glucose entry and absorption in the intestine, provoking excessive insulin response to a meal. This may occur within 1-3 hours after a meal. Very rare cases of idiopathic alimentary hypoglycemia occur in patients who have not had GI operations.

Congenital enzyme deficiencies include hereditary fructose intolerance, galactosemia, and leucine sensitivity of childhood. In hereditary fructose intolerance and galactosemia, an inherited deficiency of a hepatic enzyme causes acute inhibition of hepatic glucose output when fructose or galactose is ingested. Leucine provokes an exaggerated insulin secretory response to a meal and reactive hypoglycemia in patients with leucine sensitivity of childhood.

Other causes of hypoglycemia include the following, singly or in combination (eg, chronic renal failure and sulfonylurea ingestion):

- Autoimmune hypoglycemia: Insulin antibodies and insulin receptor antibodies
- Hormonal deficiencies: Hypoadrenalism (cortisol), hypopituitarism (growth hormone) (in children), glucagons deficiency (rare), and epinephrine (very rare)
- Critical illnesses: Cardiac, hepatic, and renal diseases; sepsis with multiorgan failure
- Exercise (in patients with diabetes treated with diabetes medications)
- Pregnancy
- Renal glycosuria
- Ketotic hypoglycemia of childhood
- Adrenal insufficiency
- Hypopituitarism

- Starvation
- Artifact

Epidemiology

The incidence of hypoglycemia in a population is difficult to ascertain. Patients and physicians frequently attribute symptoms (eg, anxiety, irritability, hunger) to hypoglycemia without documenting the presence of low blood sugar. The true prevalence of hypoglycemia, with blood sugar levels below 50 mg/dL, is generally 5-10% of people presenting with symptoms suggestive of hypoglycemia.

Hypoglycemia is a known complication of several medications, and the incidence is difficult to determine with any certainty. In addition, this condition is a known complication of many therapies for diabetes; therefore, the incidence of hypoglycemia in a population of people with diabetes is very different from that in a population of people without diabetes. [6, 7, 8, 9, 10, 11]

Insulin-producing tumors are a rare but important treatable cause of hypoglycemia, with an annual US incidence of 1-2 cases per million persons per year.

Reactive hypoglycemia is reported most frequently by women aged 25-35 years; however, other causes of hypoglycemia are not associated with a sex predilection. The average age of a patient diagnosed with an insulinoma is the early 40s, but cases have been reported in patients ranging from birth to age 80 years. [12]

Prognosis

The prognosis of hypoglycemia depends on the cause of this condition, its severity, and its duration. If the cause of fasting hypoglycemia is identified and treated early, the prognosis is excellent. If the problem is not curable, such as an inoperable malignant tumor, the long-term prognosis is poor. However, note that these tumors may progress rather slowly. Severe and prolonged hypoglycemia can be life threatening and may be associated with increased mortality in patients with diabetes.

If the patient has reactive hypoglycemia, symptoms often spontaneously improve over time, and the long-term prognosis is very good. Reactive hypoglycemia is often treated successfully with dietary changes and is associated with minimal morbidity. Mortality is not observed. Untreated reactive hypoglycemia may cause significant discomfort to the patient, but long-term sequelae are not likely.

A study by Boucai et al found that drug-associated hypoglycemia was not associated with increased mortality risk among patients admitted to general wards. This suggests that hypoglycemia may be a marker of disease burden and not a direct cause of death. [13]

Clinical Presentation