HYPOGLYCEMIA

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CLINICAL RECOGNITION

Hypoglycemia is uncommon in people who are not being treated for diabetes mellitus. Low blood glucose concentrations lead to adrenergic activation and neuroglycopenia (Table 1). Symptomatic hypoglycemia is diagnosed clinically using Whipple's triad: symptoms of hypoglycemia, plasma glucose concentration<55 mg/dl (3.0 mmol/l), and resolution of those symptoms after the plasma glucose concentration is raised. Capillary blood glucose measurements should not be used in the evaluation of hypoglycemia due to poor accuracy.

Table 1. Symptoms of Hypoglycemia

Adrenergic	Neuroglycopenic
Sweating	Behavioral changes
Warmth	Changes in vision or speech
Anxiety	Confusion
Tremor	Dizziness
Nausea	Lethargy
Palpitations	Seizure
Tachycardia	Loss of consciousness
Hunger	Coma

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Hypoglycemia in diabetes is typically the result of treatments that raise insulin levels and thus lower plasma glucose concentrations (Table 2). In adults not taking glucose-lowering drugs to treat diabetes mellitus, critical illnesses, hormone deficiencies, and islet and non-islet cell tumors should be considered.

Table 2. Causes of Adult-Onset Hypoglycemia
Drugs - see Table 3
Hepatic, renal or cardiac failure
Sepsis, trauma, burns
Malnutrition
Hormonal deficiencies (cortisol, glucagon, epinephrine)
Non-islet cell tumors (IGF-II secreting tumors)
Insulinoma (insulin-secreting tumors)
Non-insulinoma pancreatogenous hypoglycemia (NIPHS)
Post gastric bypass surgery
Post total pancreatectomy with islet auto-transplantation
Dumping syndrome or rapid gastric emptying
Insulin antibodies
Insulin receptor antibodies
Accidental, surreptitious or malicious including Munchausen syndrome by proxy

Adapted from: Cryer, PE, et al. Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 94:709-728, 2009.

Table 3. Drugs Reported to Cause Hypoglycemia
Insulin
Insulin secretagogues (especially sulfonylureas, meglitinides)
Alcohol
Cibenzoline
Glucagon (during endoscopy)
Indomethacin
Pentamidine
Sulfonamides
Quinine

Hydroxychloroquine
Artesunate/artemisin/artemether
Chloroquineoxaline
IGF-1
Lithium
Propoxyphene/dextropropoxyphene
Salicylates
The following are supported by very low-quality evidence:
Angiotensin converting enzyme inhibitors
Angiotensin receptor antagonists
Nonselective β-adrenergic receptor antagonists
Fluoroquinolones
Gabapentin
Mifepristone
Disopyramide
Trimethoprim-sulfamethoxazole
Heparin
6-Mercaptopurine

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PATHOPHYSIOLOGY

Glucose is an obligate fuel for the brain under physiologic conditions. In order to maintain proper brain function, plasma glucose must be maintained within a relatively narrow range. Redundant counter-regulatory mechanisms are in place to prevent or correct hypoglycemia. As glucose levels decline, major defenses include: 1) a decrease in insulin secretion; 2) an increase in glucagon secretion; 3) an increase in epinephrine secretion. Increased cortisol and growth hormone secretion also occur. If these defenses fail, plasma glucose levels will continue to fall. Symptoms, prompting food ingestion, typically develop at a plasma glucose of 55 mg/dl (3.0 mmol/liter). At glucose levels of 55 mg/dl and lower, insulin secretion is normally almost completely suppressed.

In longstanding type 1 and type 2 diabetes these counter-regulatory responses to hypoglycemia are

impaired. This increases the risk of hypoglycemia and also contributes to hypoglycemia unawareness.

DIAGNOSTIC TESTS

If the cause of the hypoglycemia is not evident, measure plasma glucose, insulin, c-peptide, proinsulin, and beta-hydroxybutyrate concentrations and screen for oral hypoglycemic agents (sulfonylurea and meglitinide drugs) during an episode of spontaneous hypoglycemia. Glucagon, 1 mg IV, should then be administered, with a rise in glucose >25 mg/dl (1.4 mmol/L) suggesting hyperinsulinemic hypoglycemia. The diagnosis of insulinoma is supported if insulin, c-peptide and proinsulin levels are elevated, beta-hydroxybutyrate is <2.7 mmol/l, and sulfonylurea/meglitinide levels are undetectable during the hypoglycemic episode.

If testing cannot be performed during a spontaneous episode of hypoglycemia, a 72 hour fast or a mixed meal test, performed in a monitored setting, followed by administration of glucagon is the most useful diagnostic strategy.

During a 72 hour fast, patients are allowed no food but can consume non-caloric caffeine-free beverages. Insulin, c-peptide and glucose samples are obtained at the beginning of the fast and every 4-6 hours. When the plasma glucose falls to <60 mg/dl, specimens should be taken every 1-2 hours under close supervision. Patients should continue activity when they are awake. The fast continues until the plasma glucose falls below 45 mg/dl (2.5 mmol/l) [plasma glucose <55 mg/dl (3.0 mmol/l) is recommended in the Endocrine Society guidelines] and symptoms of neuroglucopenia develop, at which time insulin, glucose, c-peptide, oral insulin secretagogue, proinsulin, and beta-hydroxybutyrate levels are obtained and the fast is terminated. Additional samples for insulin antibodies, anti-insulin receptor antibodies, IGF-1/IGF-2, and plasma cortisol, glucagon or growth hormone can also be obtained at this time if a non-islet cell tumor, autoimmune etiology, or hormone deficiency is suspected. Patients are fed at the conclusion of the fast.

For patients with hypoglycemic symptoms several hours after meals, a mixed meal test may be performed. This test has not been well standardized. Patients eat a meal similar to one that provokes their symptoms, or a commercial mixed meal. Samples for plasma glucose, insulin, c-peptide, and proinsulin are collected prior to the meal and every 30 minutes thereafter for 5 hours. If symptoms occur prior to the end of the test then additional samples for the above are collected prior to administration of carbohydrates. If Whipple's triad is demonstrated, testing for oral hypoglycemic drugs and testing for insulin antibodies should be done. Interpretation of test results is the same as for the 72-hour fast or spontaneous hypoglycemia (Table 4).

Table 4. Distinguishing Causes of Symptomatic Hypoglycemia After a Prolonged Fast

Insulin (μU/ml)	C-peptide (nmol/L)	Proinsulin (pmol/L)	Oral hypoglycemic	Interpretation
»3	<0.2	<5	No	Exogenous insulin
≥3	≥0.2	≥5	No	Endogenous insulin[a]
≥3	≥0.2	≥5	Yes	Oral hypoglycemic drug

a- Insulinoma, non-insulinoma pancreatogenous hypoglycemia (NIPHS), post gastric bypass surgery.

Adapted from: Cryer, PE, et al. Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 94:709-728, 2009

In a patient with documented hypoglycemia with laboratory findings consistent with endogenous hyperinsulinism localizing studies should be done to evaluate for insulinoma. These may include computed tomography (CT) or magnetic resonance imaging, transabdominal and endoscopic ultrasonography, and, where available, new nuclear medicine scans (GLP-1 receptor imaging), somatostatin receptor imaging SPECT / PET, and 6-[fluoride-18] fluoro-levodopa-PET-CT. If the diagnosis remains unclear, selective pancreatic arterial calcium injections with measurements of hepatic venous insulin levels can be performed.

TREATMENT

Immediate treatment should be focused on reversing the hypoglycemia. If the patient is able to ingest carbohydrates 15 to 20 grams of glucose should be given every 15 minutes until the hypoglycemia has resolved. If the patient is unable to ingest carbohydrates, or if the hypoglycemic episode is severe then parenteral glucose should be administered. In a healthcare setting intravenous dextrose is used. Twenty-five-gram boluses of 50% dextrose are given until the hypoglycemia has resolved. If needed, an infusion of 10% or 20% dextrose can be used to sustain euglycemia in patients with recurrent episodes of hypoglycemia. In the outpatient setting, glucagon is used to correct hypoglycemia. Glucose gel and other forms of oral glucose should be used in impaired patients with caution and only in circumstances where no alternative is available, as they pose an aspiration risk.

Long-term treatment should be tailored to the specific hypoglycemic disorder, taking into account the burden of hypoglycemia on well-being and patient preferences. Offending medications should be discontinued and underlying illnesses treated, whenever possible.

Surgical resection can be curative for insulinomas, and can alleviate hypoglycemia in non-islet cell tumors, even if the malignancy cannot be cured. Partial pancreatectomy can be considered in patients with β-cell disorders. Medical treatment with frequent feedings, α-glucosidase inhibitors, diazoxide, or octreotide can be used if resection is not possible, or as a temporizing measure. New drugs that may be helpful include long-acting somatostatin analogs, mTOR inhibitors, and GLP-1 antagonists. Autoimmune hypoglycemic conditions may be treated with either glucocorticoids or immunosuppressants, but these disorders may be self-limited.

For adults taking insulin or insulin secretagogues for diabetes mellitus risk factors for hypoglycemia, such as advanced age and renal insufficiency, should be considered. The treatment regimen and glycemic goals should be reviewed and adjusted if needed. Patients should be instructed on how to manage hypoglycemia, either by the ingestion of carbohydrates if possible, or by parenteral glucagon or glucose. If the patient has hypoglycemia unawareness, a 2-to 3-week period of strict avoidance of hypoglycemia should be maintained, as hypoglycemia awareness will return in many patients. For individuals with type 1 diabetes and a history of serious hypoglycemia, the use of a personal continuous glucose monitoring device, sensor-augmented insulin pump therapy, or a hybrid closed loop system should be considered.

GUIDELINES

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