### Hormone Deficiencies

Deficiencies of insulin counter-regulatory hormones, which normally function to raise glucose levels, can result in or contribute to hypoglycemia. An example is low levels of corticosteroids caused by primary or secondary adrenocorticoid insufficiency. Deficiencies of other hormones, including catecholamines, glucagon, and growth hormone, also can cause hypoglycemia.

### Severe Illness

Hypoglycemia can occur during severe illness through a number of different mechanisms in association with sepsis, hepatic insufficiency, and renal failure. Patients with severe illness appear to be particularly vulnerable to hypoglycemia when they are poorly nourished, although malnutrition alone is rarely associated with hypoglycemia.

## Approach to the Diagnosis

For patients who have well-documented hypoglycemia, the diagnosis often is evident or strongly suggested by the clinical setting, history, and physical examination findings. Hypoglycemia induced by insulin or other glucose-lowering agents in diabetic patients often is immediately apparent from the medical history. Alcohol-induced hypoglycemia may be suspected in a patient with a known or suspected history of alcohol abuse and binge drinking. Identification of other candidate drugs as a cause of hypoglycemia requires a thorough medical history, and the condition can be expected to resolve if the suspect medication is stopped. The patient may have a known diagnosis of adrenal insufficiency, or this may be suggested by other clinical findings (e.g., orthostatic hypotension, increased skin pigmentation) or the development of markedly increased insulin sensitivity in a patient with T1DM. The patient may have a known tumor suggesting the possibility of a non–islet cell neoplasm as a cause of hypoglycemia. There may be a history of Roux-en-Y bypass surgery, raising the possibility of beta-cell hyperplasia. The co-occurrence of sepsis, hepatic failure, renal failure, profound malnutrition, or a known diagnosis of anorexia nervosa may suggest one of these potential underlying causes.

A number of algorithms have been developed to guide the evaluation of documented or potential hypoglycemia, including a recommended approach from an expert panel published by the Endocrine Society. If there is an opportunity to observe the patient during a symptomatic episode of presumed hypoglycemia, plasma should be obtained, if possible before treatment, for measurement of glucose, insulin, proinsulin, C-peptide, β-hydroxybutyrate, and screening for sulfonylureas and meglitinides. Hypoglycemia can be rapidly, provisionally confirmed with a test meter. After blood samples have been obtained for the tests described, glucose should be administered orally (15 to 30 g) or intravenously (25 g, or 1 ampule of 50% dextrose), and recovery of glucose levels and symptoms should be observed.

For patients with suspected or confirmed hypoglycemia developing specifically in the fasted state, it may be possible to replicate the condition by observing during several hours of daytime fasting, with or without a preceding overnight fast. The same laboratory testing panel as described earlier then can be obtained if symptoms suggestive of hypoglycemia occur. For patients who describe postprandial hypoglycemic symptoms (within 5 hours after a meal), a mixed meal (not a pure glucose load) should be provided, with blood sampling at baseline and every 30 minutes thereafter for 5 hours

For patients who do not manifest hypoglycemia with the testing procedures described despite a strong suspicion of hypoglycemia, the most frequently utilized approach is a 72-hour fast according to a protocol developed at the Mayo Clinic. Blood is obtained every 6 hours and at test termination. The test is ended at 72 hours or at an earlier time point if the plasma glucose level decreases (by glucose meter testing) with associated symptoms to 45 mg/dL (2.5 mmol/L) or lower or to less than 55 mg/dL (3 mmol/L) in a patient with prior documentation of Whipple's triad. At the end of the 72-hour test period, the patient is given 1 mg of glucagon intravenously, and blood is obtained at 10, 20, and 30 minutes, after which the patient is given a meal. The final blood sample obtained at the end of the fast (before glucagon administration) is analyzed additionally for β-hydroxybutyrate and a sulfonylurea/meglitinide panel.

For any of these test protocols, elevations of insulin, proinsulin, and C-peptide associated with hypoglycemia at the same time point are consistent with an insulinoma, beta-cell hyperplasia, the effects of an insulin secretagogue (sulfonylurea or meglitinide), or the presence of insulin antibodies. An elevation in these three hormones during a meal test in a patient who has had gastric surgery is suggestive of alimentary hypoglycemia. Plasma insulin, proinsulin, and C-peptide are not elevated in patients with hypoglycemia secondary to extrapancreatic neoplasms. This diagnosis usually can be further confirmed by evidence of a large tumor with various imaging techniques. High insulin levels, together with low proinsulin and C-peptide concentrations in the presence of hypoglycemia, is indicative of exogenous insulin administration. Factitious hypoglycemia secondary to insulin or insulin secretagogue administration is uncommon and has been observed in individuals with or without diabetes.

## Treatment

The most important therapeutic step in hypoglycemia is to identify and treat the underlying causes, including drugs, alcohol, serious infection, tumors, and hypoadrenalism. The occurrence of hypoglycemia usually can be substantially improved in patients with alimentary hypoglycemia by a modified feeding regimen with frequent, small meals and avoidance of concentrated sources of rapidly digested and absorbed carbohydrate.

Non–islet cell tumor hypoglycemia is treated by tumor resection if possible. For nonresectable tumors, a debulking procedure may be effective in reducing hypoglycemia. Hypoglycemia in patients with insulinomas can be cured by resection. Persistent hypoglycemia secondary to nonresectable insulinoma can sometimes be treated effectively with diazoxide, long-acting somatostatin analogues (octreotide or lanreotide), verapamil, or phenytoin. For patients with beta-cell hyperplasia after bariatric surgery, first-line treatment includes diet modifications with more frequent, small meals and avoidance of concentrated sources of carbohydrate to decrease meal-induced insulin secretion.