

REVIEW ARTICLE

MEDICAL PROGRESS

HYPOGLYCEMIC DISORDERS

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HYPOGLYCEMIA is a clinical syndrome with diverse causes in which low levels of plasma glucose eventually lead to neuroglycopenia. This review will be devoted to hypoglycemic disorders that do not result from the treatment of diabetes mellitus.

GLUCOSE COUNTERREGULATION

In healthy persons, postabsorptive levels of plasma glucose stay within a narrow range (about 60 to 100 mg per deciliter [3.3 to 5.6 mmol per liter]) despite the intermittent ingestion of food. Insulin, the primary regulatory hormone that blunts postprandial hyperglycemia and maintains postabsorptive euglycemia, has its effects counterbalanced by several factors that provide a minimal level of glycemia in order to sustain the nutrition of the central nervous system. An uninterrupted flow of glucose in the blood is essential for normal metabolism in the brain.¹

Studies of insulin-induced hypoglycemia in healthy volunteers suggest a hierarchy of responses among the physiologic factors that act to counterbalance declining levels of glycemia (Fig. 1).²⁻⁴ The glycemic thresholds for the activation of these counterregulatory factors are higher than those for the development of symptoms and the impairment of cognitive function.³ Each factor's place in the hierarchy of counterregulatory forces represents the physiologic importance of that factor in defending against acute hypoglycemia.⁴⁻⁷ Glucagon provides the primary defense against hypoglycemia; without it, full recovery does not occur. Epinephrine is not necessary for counterregulation when glucagon is present. In the absence of glucagon, however, epinephrine has an important role. In contrast, hypoglycemia after an overnight fast, a 72-hour fast, or a meal cannot be generated by a deficiency of glucagon or epinephrine alone; deficiencies of both are required.^{4,8-10}

Neither growth hormone nor cortisol appears to contribute substantially to glucose counterregulation during acute insulin-induced hypoglycemia.⁴ During prolonged insulin-induced hypoglycemia — approximately 12 hours in length — deficiencies of cortisol and growth hormone in the blood result in lower plasma glucose concentrations, though they do not impair recovery from hypoglycemia.^{4,11-13} It should be pointed

out that the effects of counterregulatory hormones on glucose homeostasis in studies of insulin-induced hypoglycemia may be different from those effects in clinical situations, in which hypoglycemia is caused by a deficiency of a counterregulatory hormone without insulin mediation.

SYMPTOMS

During acute insulin-induced hypoglycemia in healthy persons, symptoms have been recognized at plasma glucose levels of approximately 60 mg per deciliter as measured in arterialized venous blood, and impairment of brain function has occurred at approximately 50 mg per deciliter (2.8 mmol per liter).²⁻⁴ Comparable levels in venous blood could be expected to be about 3 mg per deciliter (0.17 mmol per liter) lower.¹⁴ The rate at which the plasma glucose level decreases does not influence the occurrence of the symptoms and signs of hypoglycemia.^{15,16}

The symptoms of hypoglycemia have been classified into two major groups: those that arise from the action of the autonomic nervous system and those related to an insufficient supply of glucose to the brain (neuroglycopenia). In which of these two groups researchers classify particular symptoms may depend on whether or not patients have diabetes, whether the diabetes is insulin-dependent, whether the hypoglycemia is clinical or experimental, and probably most important, on patients' differing perceptions of symptoms.¹⁷ During experimentally induced hypoglycemia in 20 diabetic and 25 nondiabetic persons, a principal-components analy-

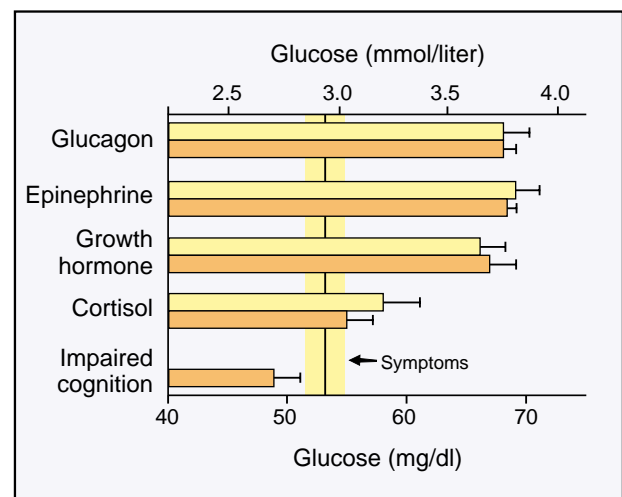


Figure 1. Threshold Plasma Glucose Levels at Which Plasma Levels of Glucagon, Epinephrine, Growth Hormone, and Cortisol Increase, Cognition Is Impaired, and Symptoms of Hypoglycemia Occur in Normal Subjects.

Yellow bars represent data from Schwartz et al.,² and orange bars data from Mitrakou et al.³ The values shown represent means (\pm SE) measured in arterialized venous blood. Reprinted from Cryer,⁴ with the permission of the publisher.

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sis assigned sweating, trembling, feelings of warmth, anxiety, and nausea to the autonomic symptom group and dizziness, confusion, tiredness, difficulty in speaking, headache, and inability to concentrate to the neuroglycopenic symptom group. Hunger, blurred vision, drowsiness, and weakness could not be confidently assigned to either group.¹⁸ In another study of symptoms in 10 nondiabetic persons with insulin-induced hypoglycemia, researchers assigned shaking or tremulousness, pounding of the heart, nervousness or anxiety, sweating, hunger, and tingling to the autonomic group and feelings of warmth, weakness, confusion or difficulty in thinking, and fatigue or drowsiness to the neuroglycopenic group.¹⁹ In a retrospective analysis of 60 patients with hypoglycemia caused by insulinomas, 85 percent had various combinations of diplopia, blurred vision, sweating, palpitations, and weakness; 80 percent had confusion or abnormal behavior; 53 percent had amnesia or were in a coma during the episode; and 12 percent had generalized seizures.²⁰

Despite the importance of studies designed to assess the types of symptoms associated with experimentally induced hypoglycemia, such studies cannot be expected to reproduce exactly the conditions of clinical hypoglycemia and the effects of milieu, activity, and time of day. In addition, the perception of symptoms that patients have in a clinical situation is likely to differ from the perception they report in response to probing questions during experimentally induced hypoglycemia. This phenomenon has been observed in studies of the symptoms of hypoglycemia in persons with diabetes.²¹ It is apparent that the symptoms of hypoglycemia differ for different persons but are nevertheless consistent from episode to episode for any one person.^{17,18} Furthermore, there is no consistent chronologic order to the evolution of symptoms; autonomic symptoms do not always precede neuroglycopenic ones. In many patients, neuroglycopenic symptoms are the only ones observed.¹⁸ An additional factor that influences the generation of symptoms in hypoglycemia is their blunting by earlier episodes of the condition. This effect has been experimentally demonstrated both in healthy subjects and in persons with hypoglycemic disorders, such as insulinomas.²²⁻²⁵ Unfortunately, there are few prospective studies of the symptoms that arise during spontaneous episodes of hypoglycemia in persons with hypoglycemic disorders other than diabetes.

CLASSIFICATION

There has been a generally held view, espoused by most writers on the subject, including myself, that hypoglycemic disorders can be divided into two major classes: those that occur in the food-deprived state and those that occur soon after the ingestion of food. In its simplest form, this classification considers the first class to comprise organic diseases, manifested primarily by neuroglycopenic symptoms, and the second to arise from functional disturbances, which lead to autonomic symptoms. This classification is no longer useful because it neither expedites diagnosis nor facilitates

an understanding of the pathophysiology of these disorders.

The conditions that have been associated with food deprivation, such as insulinomas, may in fact produce symptoms postprandially as well as during fasting. In a very few patients they occur only after food ingestion.^{26,27} Persons with factitious hypoglycemia have erratically occurring symptoms independently of food ingestion. Moreover, many hypoglycemic disorders stimulated by the ingestion of food, such as galactosemia, hereditary fructose intolerance, and ackee-fruit poisoning, can result in neuroglycopenic symptoms.^{28,29} The strongest challenge to the established classification of hypoglycemic disorders comes from the contention that a group of disorders that supposedly arises from a functional disturbance of glucose homeostasis and produces only autonomic symptoms does not, in fact, exist. There is no convincing scientific evidence that supports the diagnoses — however long in use — of functional hypoglycemia, early-diabetes hypoglycemia, and alimentary hypoglycemia.³⁰⁻³⁴ The existence of these disorders had been predicated on the now discredited five-hour oral glucose-tolerance test.³² Persons who supposedly had these disorders almost never had hypoglycemia confirmed by the measurement of blood glucose levels during episodes of spontaneous symptoms.³³⁻³⁵

For want of a better term, persons with vague symptoms after food ingestion have been said to have idiopathic postprandial syndrome. Whatever mechanism is at work in these patients, it is not hypoglycemia.³⁶ Efforts to classify such patients according to differences in their counterregulatory hormone response to the oral administration of glucose have been unsuccessful.³⁷⁻³⁹ There are no bona fide hypoglycemic disorders characterized solely by autonomic symptoms. Although some episodes of illness in persons with true hypoglycemic disorders may be sufficiently mild to generate only this type of symptom, eventually episodes of neuroglycopenia will also occur.

A more useful approach for the practitioner is a classification based on clinical characteristics (Table 1). Persons who appear healthy are likely to have different hypoglycemic disorders from persons who are ill. Hospitalized patients are at additional risk for hypoglycemia, often from iatrogenic factors. The potential for drug-induced episodes of hypoglycemia exists in any patient with the condition. These episodes may result from accidental drug ingestion in healthy persons, the mistaken dispensing of a sulfonylurea, or the idiosyncratic actions of some of the drugs used in the treatment of seriously ill patients. The occurrence of hypoglycemia in a patient with an illness associated with that condition requires little if any investigation of its cause, only a recognition of the association of the disease with a risk of hypoglycemia. Healthy-appearing persons of all ages and both sexes, for example, are at risk for insulinomas. Factitious hypoglycemia due to self-administered insulin is often seen in female health care workers. These clinical patterns serve as clues in

Table 1. Clinical Classification of Hypoglycemic Disorders.

Healthy-appearing patient	
No coexisting disease	
Cause or predisposing condition	
Drugs	
Ethanol ⁴⁰	
Salicylates ⁴¹	
Quinine ⁴²	
Haloperidol ⁴³	
Insulinoma ⁴⁴	
Factitious hypoglycemia induced by insulin ⁴⁵	
Intense exercise ⁴⁶	
Ketotic hypoglycemia ⁴⁷	
Coexisting disease under treatment	
Cause or predisposing condition	
Drugs	
Dispensing error ^{48,50}	
Disopyramide ⁵¹	
β -adrenergic-blocking agents ⁵²	
Drugs containing sulfhydryl or thiol and autoimmune insulin syndrome ⁵³	
Ackee-fruit poisoning and undernutrition ⁵⁹	
Ill-appearing patient	
Cause or predisposing condition	
Drugs	
Pentamidine for pneumocystis pneumonia ⁵⁴	
Trimethoprim-sulfamethoxazole and renal failure ⁵⁵	
Propoxyphene and renal failure ⁵⁶	
Quinine for cerebral malaria ⁵⁷	
Quinidine for malaria ⁵⁸	
Topical salicylates and renal failure ⁵⁹	
Illness or condition	
Small size for gestational age in infants ⁶⁰	
Beckwith-Wiedemann syndrome ⁶¹	
Erythroblastosis fetalis ⁶²	
Hyperinsulinemia in infants due to maternal diabetes ⁶³	
Glycogen storage disease ⁶⁴	
Defects in amino acid and fatty acid metabolism ⁶⁵	
Reye's syndrome ⁶⁶	
Cyanotic congenital heart disease ⁶⁷	
Hypopituitarism ⁶⁸	
Isolated growth hormone deficiency ⁶⁹	
Isolated corticotropin deficiency ⁷⁰	
Addison's disease ⁶⁸	
Galactosemia ²⁸	
Hereditary fructose intolerance ²⁸	
Carnitine deficiency ⁷¹	
Defective type 1 glucose transporter in the brain ⁷²	
Acquired severe liver disease ⁷³	
Large non- β -cell tumor ⁷⁴	
Sepsis ⁷⁵	
Renal failure ⁷⁶	
Congestive heart failure ⁷⁷	
Lactic acidosis ⁷⁸	
Starvation ⁷⁹	
Anorexia nervosa ⁸⁰	
Surgical removal of pheochromocytoma ⁸¹	
Insulin-antibody hypoglycemia ⁸²	
Hospitalized patient	
Cause or predisposing condition	
Hospitalization for a predisposing illness	
Total parenteral nutrition and insulin therapy ⁸³	
Interference of cholestyramine with glucocorticoid absorption ⁸⁴	
Shock ⁸³	

making the differential diagnosis and in directing the diagnostic evaluation.

Patients may have a history of neuroglycopenic spells or may be observed during a hypoglycemic episode. Asymptomatic patients may have artifactual hypoglycemia due to leukemia⁸⁵ or severe hemolysis⁸⁶ or may have adapted to lifelong hypoglycemia caused by glycogen storage disease.⁸⁷ In the past 18 months, function-

ing benign insulinomas have been removed from two patients at the Mayo Clinic who had absolutely no symptoms, despite low concentrations of plasma glucose during ordinary activity. Each had neuroglycopenic symptoms for the first time during a 72-hour fast. The serendipitous discovery of low plasma glucose concentrations, despite the absence of symptoms, warranted evaluation.

EVALUATION

The direction and extent of evaluation depend on the clinical presentation. A healthy-appearing patient with no coexisting disease who has a history of episodic symptoms suggestive of hypoglycemia requires an approach quite different from that taken with a hospitalized patient with acute hypoglycemia.

THE HEALTHY-APPEARING PATIENT

Plasma Glucose Levels

Because symptoms of hypoglycemia are nonspecific, it is necessary to verify that there is a low plasma glucose level at the time spontaneous symptoms occur and that symptoms are relieved through correction of the low glucose level ("Whipple's triad"⁸⁸) before concluding that a patient has a hypoglycemic disorder. Furthermore, to rely solely on a low plasma glucose level to diagnose a hypoglycemic disorder fails to take into consideration the chances of laboratory error or artifactual hypoglycemia or, indeed, the possibility that normal persons may have plasma glucose levels well below 50 mg per deciliter⁸⁹ while fasting. When plasma glucose has been measured with reliable monitoring techniques in persons with postprandial symptoms, hypoglycemia has almost invariably been ruled out as a cause of symptoms.³³⁻³⁵ A normal plasma glucose level, reliably obtained during the occurrence of spontaneous symptoms, eliminates the possibility of a hypoglycemic disorder; no further evaluation is required. Although hypoglycemic disorders are uncommon, symptoms suggestive of hypoglycemia are quite common. Glucose measurements made by the patient with a reflectance meter during the occurrence of spontaneous symptoms are likely to provide false information. Patients are usually not experienced in this technique; the measurements are obtained under adverse circumstances — while the patient is symptomatic — and the method may not even provide an accurate measurement of glucose levels in the hypoglycemic range.⁹⁰

Often, measurement of the plasma glucose level is not feasible when spontaneous symptoms occur during the activities of ordinary life. Under such circumstances, a judgment by the physician whether to proceed with further evaluation depends on a detailed history. A history of neuroglycopenic symptoms or a confirmed low plasma glucose level warrants further testing.

The 72-Hour Fast

The supervised 72-hour fast is the classic diagnostic test for hypoglycemia. It should be conducted in a hospital following standardized procedures. A suggested protocol is shown in Table 2. For patients who have nei-

Table 2. Protocol for 72-Hour Fast.

ther symptoms or signs of hypoglycemia nor severely depressed plasma glucose concentrations (below 40 mg per deciliter [2.2 mmol per liter]), the fast should be concluded after 72 hours. Fasting, however, should be terminated when patients have symptoms similar to those that occurred during the activities of ordinary life and simultaneously have plasma glucose levels in the hypoglycemic range.

The decision to end the fast may not be easy for the house officer to make. Because of possible delays in the availability of the results of plasma glucose testing, the bedside reflectance meter may have to serve as a guide to glucose levels. Some patients have slightly depressed glycemic levels without symptoms or signs of hypoglycemia. Other patients may reproduce during fasting the symptoms they experienced in ordinary life, but may have plasma glucose levels that are sometimes in and sometimes above the hypoglycemic range. In such instances the attribution of symptoms to hypoglycemia is difficult, especially if all additional measure-

ments made during fasting are normal. To complicate matters, young, lean, healthy women may have plasma glucose levels in the range of 40 mg per deciliter or even lower.⁸⁹ Careful examination and testing for subtle signs or symptoms of hypoglycemia should be conducted repeatedly when the patient's plasma glucose level is near or in the hypoglycemic range. To end fasting solely on the basis of a low plasma glucose level, in the absence of symptoms or signs of hypoglycemia, jeopardizes the possibility of discriminating between normal persons and those with hypoglycemia not mediated by insulin. A suggested diagnostic interpretation of data obtained at the end of a 72-hour fast is shown in Table 3.⁹¹⁻⁹³

The absence of signs or symptoms (or both) typical of hypoglycemia during a 72-hour fast precludes the diagnosis of a hypoglycemic disorder. A low plasma glucose level is a necessary but not sufficient finding for this diagnosis. A lowered level of β -hydroxybutyrate and a vigorous plasma glucose response to intravenous glucagon point to hypoglycemia mediated by insulin or an insulin-like factor. Discrimination among the causes of insulin-mediated hypoglycemia can be made on the basis of the concentrations of beta-cell polypeptides and the detection of sulfonylurea in the plasma. Insulin, C-peptide, and proinsulin levels are increased in patients with insulinomas and sulfonylurea hypoglycemia; sulfonylurea is present in the plasma in the latter condition, but not the former. Factitious hypoglycemia produced by self-administered insulin is associated with suppressed levels of C peptide. Hypoglycemia that is not mediated by insulin or an insulin-like factor is characterized by suppressed levels of beta-cell polypeptides.

Although counterregulatory hormones have been reported to increase in normal persons fasting for 72 hours (Fig. 2),^{9,89} there are no established criteria for

Table 3. Diagnostic Interpretation of the Results of a 72-Hour Fast.*

DIAGNOSIS	SYMPTOMS OR SIGNS	GLUCOSE†	INSULIN‡§	C PEPTIDE¶	PROINSULIN§	β -HYDROXY-BUTYRATE	CHANGE IN GLUCOSE**	SULFONYLUREA IN PLASMA
		mg/dl	μ U/ml	nmol/liter	pmol/liter	mmol/liter	mg/dl	
Normal	No	≥ 40	< 6	< 0.2	< 5	> 2.7	< 25	No
Insulinoma	Yes	≤ 45	≥ 6 ††	≥ 0.2	≥ 5	≤ 2.7	≥ 25	No
Factitious hypoglycemia from insulin	Yes	≤ 45	≥ 6 ‡‡	< 0.2	< 5	≤ 2.7	≥ 25	No
Sulfonylurea-induced hypoglycemia	Yes	≤ 45	≥ 6	≥ 0.2	≥ 5	≤ 2.7	≥ 25	Yes§§
Hypoglycemia mediated by insulin-like growth factor	Yes	≤ 45	≤ 6	< 0.2	< 5	≤ 2.7	≥ 25	No
Non-insulin-mediated hypoglycemia	Yes	≤ 45	< 6	< 0.2	< 5	> 2.7	< 25	No
Inadvertent feeding during the fast	No	≥ 45	< 6	< 0.2	< 5	≤ 2.7	≥ 25	No
Nonhypoglycemic disorder	Yes	≥ 40	< 6	< 0.2	< 5	> 2.7	< 25	No

*Measurements are made at the point the decision is made to end the fast.

†Sequential plasma glucose measurements in the hypoglycemic range fluctuate. Plasma glucose levels ≤ 45 mg per deciliter at the time a decision is made to end the fast may rise to as much as 56 mg per deciliter when the fast is actually ended approximately one hour later. Plasma glucose levels may be as low as 40 mg per deciliter during prolonged fasting in normal women. To convert values to millimoles per liter, multiply by 0.05551.

‡Measured by double-antibody radioimmunoassay (lower limit of detection, 5 μ U per milliliter). To convert values to picomoles per liter, multiply by 6.0.

§In normal subjects plasma insulin, C-peptide, and proinsulin levels may be higher if the plasma glucose level is ≥ 60 mg per deciliter.

¶Measured by the immunochemiluminometric technique (lower limit of detection, 0.033 nmol per liter).

||Measured by the immunochemiluminometric technique (lower limit of detection, 0.2 pmol per liter).

**In response to intravenous glucagon (peak value minus value at end of fast). To convert values to millimoles per liter, multiply by 0.05551.

††Ratios of insulin to glucose are of no diagnostic value in patients with insulinomas.

‡‡Plasma insulin levels may be very high (> 100 μ U per milliliter or > 1000 μ U per milliliter) in factitious hypoglycemia from insulin.

§§Unlike the first generation of sulfonylurea drugs, which were easily measured, second-generation drugs are not.

the response of such hormones during the fast, especially in patients with hypoglycemic disorders. Despite some reports,⁹⁴ there has not been any convincing evidence of cases in which glucagon deficiency was a cause of hypoglycemia. Epinephrine deficiency, like that which occurs after bilateral adrenalectomy, does not predispose patients to hypoglycemia.⁴

In the chance event that a patient has a spontaneous hypoglycemic episode in the presence of medical personnel, recommended procedures for the termination of the 72-hour fast should be followed.

The C-Peptide Suppression and Intravenous Tolbutamide Tests

The C-peptide suppression test⁹⁵ and tolbutamide tolerance test⁹⁶ may be used to provide additional diag-

nostic information, especially if data from the 72-hour fast are not conclusive. These tests may also be used as screening tests: when the likelihood of a hypoglycemic disorder, although present, is not high, a normal result on these tests may preclude the need for a 72-hour fast. The C-peptide suppression test is based on the observation that beta-cell secretion (as measured by levels of C peptide) is suppressed during hypoglycemia to a lesser degree in persons with insulinomas than in normal persons. Interpretation of the C-peptide suppression test requires normative data appropriately adjusted for the patient's body-mass index and age (Fig. 3). Several criteria have been proposed for the interpretation of the intravenous tolbutamide test.⁹⁶ The C-peptide suppression test and intravenous tolbutamide test should not

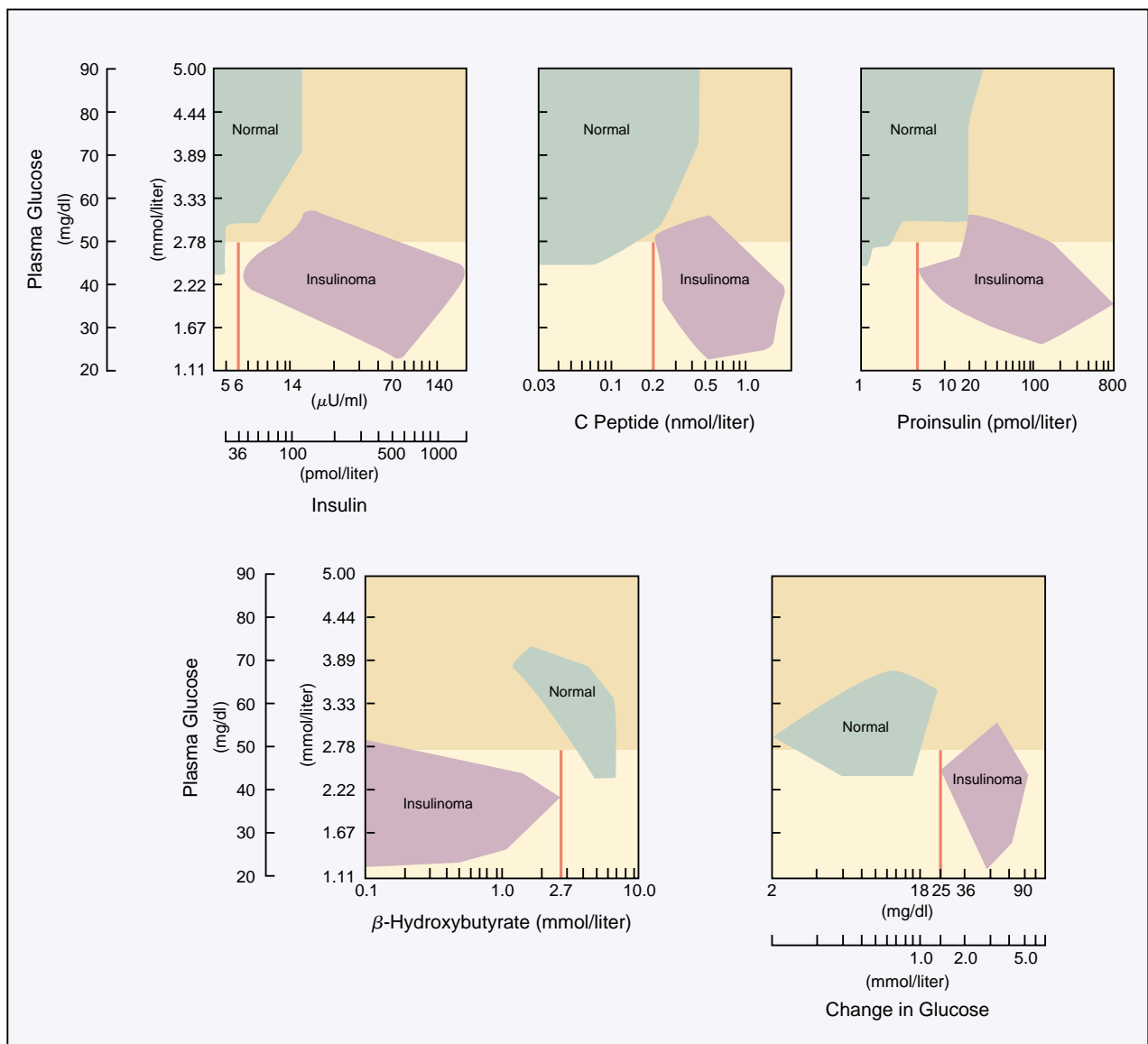


Figure 2. Limits of Plasma Insulin, C-Peptide, Proinsulin, and β -Hydroxybutyrate Levels and Changes in Plasma Glucose Levels in Response to Intravenous Glucagon, According to Plasma Glucose Levels at the End of a 72-Hour Fast in 25 Normal Persons and When the Features of Whipple's Triad Were Noted in 40 Patients with Histologically Confirmed Insulinomas.

The light yellow areas represent plasma glucose levels ≤ 50 mg per deciliter (2.8 mmol per liter). The vertical red lines represent the diagnostic criteria for insulinoma: insulin, ≥ 6 μ U per milliliter (36 pmol per liter); C peptide, ≥ 0.2 nmol per liter; proinsulin, ≥ 5 pmol per liter; β -hydroxybutyrate, ≤ 2.7 mmol per liter; and change in glucose level, ≥ 25 mg per deciliter (1.4 mmol per liter).⁹¹⁻⁹³

be administered unless the plasma glucose level exceeds 60 mg per deciliter immediately before the test. A diagnostic criterion that uses the level of glycated hemoglobin to verify the presence of a hypoglycemic disorder has not been established.

Insulin Antibodies

The detection of insulin antibodies was once considered to be firm evidence of factitious hypoglycemia due to self-administered insulin,⁹⁷ especially when animal insulin was the only commercially available type. Currently, patients with this disorder usually have no detectable insulin antibodies, possibly because of the use of human insulin, which is less antigenic than the form derived from animals. The presence of insulin antibodies has been considered to be the criterion for a diagnosis of insulin autoimmune hypoglycemia,⁵³ but antibodies may be detected in persons without hypoglycemia⁹⁸ and, in rare instances, in patients with insulinomas.⁹⁹ The detection of insulin antibodies in a patient with hypoglycemia thus sometimes serves more to confuse than to clarify the diagnosis. However, it is important to test for the presence of insulin antibodies, because they may cause spurious results on the radioimmunoassay for insulin.

The Mixed-Meal Test

For persons who have experienced symptoms soon after food ingestion (for example, two to four hours postprandially) repeated plasma glucose measurements after the ingestion of a mixed meal may confirm the history. Usually, it does not, and hypoglycemia can therefore be ruled out.³² A positive mixed-meal test calls for further evaluation for the cause of the hypoglycemia. The five-hour oral glucose-tolerance test should not be used as a diagnostic test for hypoglycemia.¹⁰⁰

THE ILL-APPEARING PATIENT

Persons with coexisting disease sometimes have discrete episodes of hypoglycemia, which may be asymptomatic if they already have blunting of consciousness. In such cases, it may be sufficient to recognize the underlying disease and its association with hypoglycemia, and to take action to minimize recurrences of the episode. Confirmation of the suspected mechanism of the hypoglycemia may be sought. Such confirmation might include finding low insulin and C-peptide levels in non-insulin-mediated hypoglycemias, such as ethanol hypoglycemia; elevated insulin-like growth factor II levels in non-beta-cell tumor hypoglycemia; low levels of cortisol in adrenal insufficiency; and blunted plasma glucose responses to intravenous glucagon in hypoglycemias due to abnormal liver function (e.g., glycogen storage disease, sepsis, and congestive heart failure).

With the progressively more restrictive limits on hospital admissions, hospitalized patients are often severely ill persons with multisystem disease. They are at risk for iatrogenic hypoglycemia as well as for any hypoglycemia that may be produced by the underlying disease. In one tertiary care medical center, 1.2 percent of all patients admitted during a six-month period had hypoglycemia, as indicated by plasma glucose levels of 49

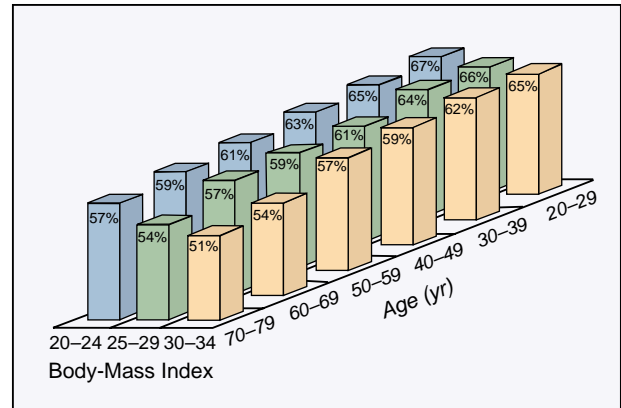


Figure 3. Normative Data for the Interpretation of the Results of the C-Peptide Suppression Test.

These data were derived from a study of 101 normal subjects in whom hypoglycemia was induced by the administration of insulin (0.125 unit per kilogram of body weight over a period of 60 minutes).⁹⁵ In each body-mass-age subgroup, 95 percent of the subjects had a level of C-peptide suppression at 60 minutes that was greater than the value shown. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. Reprinted from Service et al.,⁹⁵ with the permission of the publisher.

mg per deciliter (2.7 mmol per liter) or less. The primary causes of the hypoglycemia, in persons without diabetes, were renal insufficiency, malnutrition, liver disease, infection, and shock.⁸³ Several patients had more than one risk factor. Not infrequently, nondiabetic patients become hyperglycemic because of treatment with enteral or parenteral nutrition or glucocorticoids. The use of insulin to control hyperglycemia puts patients at risk for hypoglycemia, especially if feedings are interrupted, if the glucocorticoid dose is abruptly reduced or eliminated, or if its systemic availability is diminished by the simultaneous administration of a bile acid sequestrant.⁸⁴

In ferreting out the cause of hypoglycemia in a hospitalized, seriously ill patient, a diligent examination of the record may be more profitable than examination of the patient. For hospitalized patients, it is important to be alert to the risk of hypoglycemia, to monitor those at risk closely, and to take corrective action and provide supportive therapy should hypoglycemia develop.

MANAGEMENT

The treatment of hypoglycemic disorders encompasses two distinct components: the relief of neuroglycopenic symptoms by the restoration of the plasma glucose level to the normal range and the correction of the underlying cause. Unlike the situation in patients with diabetes, in whom the restoration of euglycemia after an episode of hypoglycemia is the ideal goal, the overtreatment of hypoglycemia in a nondiabetic person has no ill effects. If feasible, blood should be obtained by venipuncture from a patient with an as yet undiagnosed condition before treatment begins, in order to measure glucose, beta-cell polypeptides, counterregulatory hormones, and β -hydroxybutyrate. The patient may be treated with an intravenous injection of glucagon and the plasma glucose response monitored. Such

a course of action has a high likelihood of providing both diagnostic data and effective treatment. Depending on the response, patients may require intravenous glucose, administered either as a bolus of 50 percent solution or a continuous infusion of 5 percent or 10 percent solution, or they may recover sufficiently to take oral nutrition.

The approach to treatment of the underlying cause of the hypoglycemia depends on the specific causal mechanism. Once a biochemical diagnosis of an insulinoma has been made, for example, preoperative localization should be attempted. Because of the rarity of insulinomas, only a few referral centers have acquired sufficient experience to assess the effectiveness of various localization procedures. Although there is general agreement that computed tomography, magnetic resonance imaging, and celiac-axis angiography are not sufficiently sensitive in locating insulinomas,^{101,102} experts differ in their preferred approaches, most likely because of differences in their experience and skills. Transhepatic portal venous sampling for insulin, a highly invasive technique, can help identify the region — the head, body, or tail of the pancreas — where the insulinoma is located.¹⁰³ Ultrasonography has the advantage of precise localization, especially in relation to the pancreatic duct.¹⁰⁴ There is general agreement that intraoperative ultrasonography provides the highest success rate in localization.^{100,104,105} There is too little experience with octreotide scanning,¹⁰⁶ endoscopic ultrasonography,¹⁰⁷ and selective intraarterial calcium injection¹⁰⁸ for these procedures to be evaluated.

Insulinoma is a rare tumor, the incidence of which is estimated to be four cases per 1 million person-years,⁴⁴ an incidence similar to that of pheochromocytoma.¹⁰⁹ Insulinomas may occur at any age, are slightly more common in women, and are associated with low rates of cancer (6 percent), multiple endocrine neoplasia syndrome (8 percent), and recurrence (8 percent); only 9 percent of patients have multiple tumors.⁴⁴ After successful removal of an insulinoma, the patient can look forward to a normal life expectancy.⁴⁴ Medical therapy for a patient whose insulinoma was missed during pancreatic exploration, a patient found to be unsuitable for surgery, or a patient with metastatic insulinoma may include treatment with diazoxide, verapamil, phenytoin, propranolol, or octreotide.⁸² Insulinomas are occasionally suspected in patients with labile diabetes, especially when insulin therapy has been suspended. Insulinomas have not been documented in patients with insulin-dependent diabetes mellitus; they occur only rarely in the non-insulin-dependent form of the disease.¹¹⁰

Factitious hypoglycemia due to surreptitious insulin administration is usually manifested by erratically occurring neuroglycopenic symptoms. This disorder is observed more often in women, usually those in a health-related occupation. Once confronted with the diagnosis, about half the patients acknowledge giving themselves the drug; most subsequently cease the activity.⁴⁵ Insulin autoimmune hypoglycemia may be very difficult to distinguish from factitious hypoglycemia,

because of their similar biochemical features.¹¹¹ However, many patients with the former condition have other evidence of autoimmune disease.¹¹² Autoimmune insulin hypoglycemia appears to be self-limiting.

In instances of drug-induced hypoglycemia, the offending medication should be eliminated immediately. Frequent feedings may be sufficient to sustain euglycemia in cases of ketotic hypoglycemia, but nocturnal intragastric infusions of solutions containing glucose²⁸ or cornstarch¹¹³ may be needed in cases of glycogen storage disease. If feasible, large nonpancreatic tumors causing hypoglycemia should be removed or reduced in size.

The diagnosis of a hypoglycemic disorder requires a high level of suspicion, careful assessment of the patient for the presence of mediating drugs or a predisposing illness, and, where indicated, methodical evaluation on the basis of well-defined diagnostic criteria.

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