Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Volume 33, Number 12 / May 21, 2012 www.emreports.com

Authors:

Cara O'Shaughnessey, DO, Diabetes Fellow, Ohio University Heritage College of Osteopathic Medicine, O'Bleness Health System, Athens, OH

Jay H. Shubrook, Jr., DO, **FACOFP, FAAFP,** Associate Professor of Family Medicine and Director of Diabetes Fellowship, Ohio University Heritage College of Osteopathic Medicine, Athens, OH

Peer Reviewer:

Ademola Adewale, MD, FAAEM, Director of Research and Medical Simulation, Assistant Program Director, Florida Hospital Emergency Medicine Residency, Orlando, FL

Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Farel (CME question reviewer) owns stock in Johnson & Johnson. Dr. Stapczynski (editor) owns stock in Bristol Myers Squibb. Dr. Schneider (editor), Dr. O'Shaughnessy (author), Dr. Shubrook (author), Dr. Adewale (peer reviewer), Dr. Wise (editor), Ms. Coplin (executive editor), and Ms. Kimball (managing editor) report no financial relationships relevant to this field of study, Ms. Mark (executive editor), and Ms. Hamlin (managing editor) report no financial relationships with companies related to the field of study covered by this CME activity.

AHC Media

Hypoglycemia in Adults

This article is adapted from an article that originally appeared in the May 2012 issue of Primary Care Reports.

Almost every emergency physician I know has missed a case of hypoglycemia in their career. I have. I have also been practicing long enough to have used "Dextrostix." Remember using them? Remember some of the values you obtained? Sometimes the results made no sense. But while they were imperfect, at least they enabled us to sometimes detect severe hypoglycemia at the patient's bedside in the emergency department (ED) without waiting for the central laboratory. Now, we have point-of-care (POC) glucose testing, so we have increased ability to detect hypoglycemia and almost no barriers to rapid detection. This is timely, because along with the increase in the diabetic population provoked by the obesity epidemic, there is increased emphasis on glycemic control. And one complication of tighter glucose control is the increased risk for hypoglycemia. And as we all experience, patients with acute symptoms, such as those produced by hypoglycemia, are likely to come to the ED. This issue of EM Reports *is about hypoglycemia in diabetic adults, from pathophysiology to recognition and acute management, and with recommendations for follow-up.*

— J. Stephan Stapczynski, MD, Editor

Introduction

Emergency physicians are exposed to the many faces of hypoglycemia. We see it as treatment-induced hypoglycemia in patients with type 1 diabetes and in many patients with advanced type 2 diabetes.[1-4] We see hypoglycemia caused by non-hypoglycemic drugs and toxins. We see it in patients with chronic liver or renal disease. We see hypoglycemia in sepsis and septic shock. We may even see patients with postprandial hypoglycemia due to an imbalance between eating and insulin release. (*See Table 1.*) The presenting symptoms of hypoglycemia usually include some alteration in mental status along with an autonomic response, but may be masked or obscured with co-morbid conditions, drugs, or toxins. It is an axiom that severe, untreated hypoglycemia can be fatal, but it is also important to recognize that lesser degrees of hypoglycemia, especially if prolonged or recurrent, can produce significant morbidity.[1]

Definition

In 1938, American surgeon Allen Whipple defined hypoglycemia by the following triad: typical signs and symptoms of hypoglycemia; documented low glucose level; and correction of signs and symptoms with normalization of glucose levels.[5]

Different glucose levels have been used to characterize hypoglycemia. One difficulty with a precise defined level is the variation in symptoms and glucose levels between individuals. During fasting, some healthy adults will have serum glucose levels below 60 mg/dL and have no symptoms. Thus, there is an overlap between those who satisfy Whipple's triad as defined above and those who only have a low glucose level but without symptoms. For clinical use, a value

Executive Summary

- Hypoglycemia is defined by a triad of typical signs and symptoms, documented low blood glucose, and correction of signs and symptoms with normalization of blood glucose.
- Patients with drug-related diabetes should take defensive action when blood glucose falls below 70 mg/dL.
- Point-of-care glucose measurements may give false elevated values if the test strip is contaminated with sugar from the technician's hands or if a capillary specimen is used in critically ill patients.
- Glucagon 1 mg SC or IM should be used to treat symptomatic hypoglycemia if the patient is not able to ingest carbohydrates and IV access is not possible.
- Intravenous dextrose 25 g (1 ampule of D50) is the standard treatment for symptomatic hypoglycemia, but the response is variable and blood glucose should be assessed after administration.
- Intravenous glucose infusion with D10 is often necessary to maintain blood glucose in patients with excess insulin activity, as in an insulin for sulfonylurea overdose.
- Octreotide is effective for sulfonylurea overdose.

is usually chosen to identify nearly all the symptomatic patients with hypoglycemia and to avoid over-classification of hypoglycemia in asymptomatic patients.[6,7]

In 2005, the American Diabetes Association (ADA) Workgroup on Hypoglycemia defined hypoglycemia in patients with diabetes as "all episodes of an abnormally low plasma glucose concentration (with or without symptoms) that expose the individual to harm."[8] The workgroup recommended that patients with drug-treated diabetes should become concerned about developing hypoglycemia when their self-monitored blood glucose level is < 70 mg/dL[8] or is falling rapidly.[1] The plasma glucose concentration of 70 mg/dL was used as it approximates the lower limit of the fasting non-diabetic glucose concentration range and the normal glycemic threshold for glucose counter-regulatory hormone activation.[2] This value also is low enough to reduce glycemic defenses against further hypoglycemia in non-diabetic individuals[1,9,10] and is higher than the glycemic level required to produce symptoms of hypoglycemia (~ 55 mg/dL [3.0 mmol/L]) or impair brain function in those without diabetes.[11,12]

Despite significant advances, POC glucose meters are not always precise, especially at low plasma glucose levels,[1,13] and can have an acceptable error rate of up to 16%. Therefore, a cutoff value of 70 mg/dL provides the patient with time to prevent a symptomatic hypoglycemic episode, as well as some margin for potential inaccuracy of glucose meter readings.[1]

Table 1: Pathophysiologic Classification of Hypoglycemia in Adults

Mechanism	Drug or Toxin	During Fasting	Postprandial
Increased insulin activity	Excess insulin Sulfonylureas Cibenzoline* Gatifloxacin* Pentamidine* Quinine* Indomethacin*	Insulinoma Functional beta-cell disorders Antibodies to insulin receptor or insulin	Post GI surgery Alimentary
Liver dysfunction	Ethanol Non-selective beta-blockers	Septic shock Heart failure Multi-endocrine deficiency	Ackee fruit
Decreased substrate	Chronic renal insufficiency	Uremia Large tumors Severe wasting	
Increased glucose consumption		Prolonged exercise	
* Drugs with moderate quality of evidence for causing hypoglycemia			

The ADA Workgroup proposed a classification of hypoglycemia in diabetes that includes the following: severe, documented symptomatic, asymptomatic, probable symptomatic, and relative hypoglycemia (*see Table 2*).[8] Severe hypoglycemia requires the assistance of another individual to provide hypoglycemic treatment, but does not require the measurement of a plasma glucose level during the event.[14] Recovery of neurologic symptoms with a normal plasma glucose level provides sufficient evidence that a severe hypoglycemic event took place.

Symptomatic hypoglycemia makes up the majority of hypoglycemic episodes and can occur in people with diabetes regardless of treatment and even in people who do not have diabetes. Asymptomatic hypoglycemia is especially concerning if glucose levels are lower than 50 mg/dL or if it occurs frequently. Relative

Table 2: Types of Hypoglycemia

Type of Hypoglycemia	Glucose Level	Etiology	Related to Diabetes or Other Disease
Mild asymptomatic	< 70 mg/dL but > 50 mg/dL	Many	Sometimes related
Mild symptomatic	< 70 mg/dL but > 50 mg/dL	Many	Sometimes related
Severe hypoglycemia	< 50 mg/dL or any low glucose that requires assistance from others	Hypoglycemic agents or excessive insulin secretion	Yes
Probable hypoglycemia	Not measured	Many	Likely related
Relative hypoglycemia	> 70 mg/dL	Likely in patient with diabetes on treatment	Yes, both type 1 and type 2
Reactive hypoglycemia	Initial rise above normal after meal, followed by a 75 mg/dL drop	Altered insulin secretion — usually first phase insulin secretory defect	Can occur in prediabetics
Post-absorptive hypoglycemia	Typically drops after meals without prior rise	Altered GI transit	No — diabetes Yes — bowel disorders

hypoglycemia is most often seen in people who are chronically hyperglycemic, have become accustomed to being hyperglycemic, and then develop symptoms related to the drop in glucose, not the absolute value. (*See Table 2.*)

Frequency

Hypoglycemia occurs frequently in patients with type 1 diabetes.[2-6,15,16] The average patient with type 1 diabetes experiences two episodes of symptomatic hypoglycemia per week,[1,17] and typically one episode of severe, and at least temporarily disabling, hypoglycemia (with seizure or coma) per year.[1,17] This does not include the numerous episodes of asymptomatic hypoglycemia with plasma glucose concentrations as low as 50-60 mg/dL (2.8-3.3 mmol/L). People can be low as much as 10% of the time.[2,17] Severe hypoglycemic events have been reported to range from 62 to 170 episodes per 100 patient years in type 1 diabetes.[1,2,17-19]

Hypoglycemia also may affect patients with type 2 diabetes.[20,21] This is most likely to occur in those treated with either insulin or insulin secretagogues.[1-3,15,17] Hypoglycemia rates approach those of type 1 diabetes as the disease becomes more advanced and insulin deficiency ensues.[1-3] The UK Hypoglycemia Study Group reported that the prevalence of severe hypoglycemia in patients with type 2 diabetes treated with insulin for less than 2 years was only 7%, while the prevalence of severe hypoglycemia with type 2 diabetes more than 5 years increased to 25%.[22] The overall event rate for hypoglycemia in insulin-treated type 2 diabetes is approximately 30% of that in type 1 diabetes, according to a population-based, prospective study by Donnelly et al (1600 vs. 2400 per 100 patient-years, respectively).[17] Tight glycemic control also is associated with an increased incidence of symptomatic hypoglycemia in patients with type 2 diabetes.[23-27] Elderly (age 65 years or older) patients with type 2 diabetes have nearly twice as many hypoglycemic episodes as those younger than 65 years.[28] Thus, since there are 20 times more people with type 2 diabetes, most episodes of iatrogenic hypoglycemia will occur in patients with type 2 diabetes.

Pathophysiology

Normally, hypoglycemia is prevented or promptly ameliorated by redundant glucose counter-regulatory mechanisms.[1,12] The critical physiological mechanisms involved include a marked reduction in insulin secretion as glucose levels drop within the physiological range; an increase in glucagon secretion or epinephrine secretion (if the former is absent) as glucose levels drop just below the physiological range; and an increase in cortisol and growth hormone secretion, both occurring with prolonged hypoglycemia.[1] Plasma glucose levels will continue to drop if these defenses fail to halt the episode. When the plasma glucose concentration reaches 55 mg/dL (3.0 mmol/L) or less, hypoglycemic symptoms trigger the behavioral defense of food consumption.[1,11,12]

With the above physiologic defenses in mind, hypoglycemia in patients with type 1 or advanced type 2 diabetes is the consequence of insulin excess,[1,29] defective glucose counter-regulation (decreased ability to suppress endogenous insulin production and increase glucagon secretion),[5,6,29] or compromised behavioral defenses against falling plasma glucose concentrations.[1,16]

Early in the course of type 2 diabetes, the incidence of hypoglycemia is relatively low, even with insulin treatment, because the above glycemic defenses are intact. However, with long-standing type 2 diabetes, beta-cell failure leads to absolute endogenous insulin deficiency.[22] Patients with type 1 and advanced type 2 diabetes become critically dependent on the third defense, epinephrine secretion, because they have lost the insulin and glucagon defenses.[5,30,31] The epinephrine response to hypoglycemia often becomes attenuated in these patients,[5,30-32] leading to the clinical syndrome of compromised glucose

Table 3: Physiologic Response to Hypoglycemia

Glucose Level	Response	Result
80-85 mg/dL	Suppression of insulin secretion	Primary defense against hypoglycemia
65-70 mg/dL	Increased glucagon secretion Increased cortisol and growth hormone secretion	Primary counter-regulatory response Slower counter-regulatory response, minor role
50-55 mg/dL	Hunger	Increase in exogenous glucose
< 50 mg/dL	Neuroglycopenic symptoms	Compromised response

Table 4: Response to Hypoglycemia: Normal Vs. Diabetics

Condition	Insulin	Glucagon	Epinephrine
Normal	Sharply decreases	Increases	Increases
Early type 2 diabetes	Decreases	Increases	Increases
Late type 2 diabetes	No decrease	No increase	Attenuated increase
Type 1 diabetes	No decrease	No increase	Attenuated increase

counter-regulation and increasing the risk of severe hypoglycemia by 25-fold.[32] The glycemic thresholds for epinephrine activation can be shifted to lower plasma glucose levels due to recent and recurrent hypoglycemia,[30,31] as well as other potentially reversible factors including exercise and sleep.[2,17,33,34] (*See Tables 3 and 4.*)

The most serious form of an attenuated response to the normal defenses to hypoglycemia is the syndrome of hypoglycemia-associated autonomic failure (HAAF). It is the result of the reduced sympathoadrenal, predominantly sympathetic neural response to hypoglycemia failure.[5,33,34] The key concept of HAAF in patients with type 1 and advanced type 2 diabetes is that antecedent hypoglycemia leads to a vicious cycle of recurrent hypoglycemia by causing further impairment of glucose counter-regulation to subsequent hypoglycemia, thus leading to hypoglycemia unawareness.[1,5] HAAF is a functional disorder that can be induced by prior hypoglycemia and reversed by avoidance of hypoglycemia for at least 2-3 weeks.[5] Hypoglycemia unawareness is defined as the onset of neuroglycopenia before the appearance of autonomic warning symptoms.[35] Patients with hypoglycemia unawareness lose the adrenergic symptoms that previously triggered the behavioral defense to consume carbohydrates and correct developing hypoglycemia.[1,2]

Hypoglycemia unawareness occurs more frequently in patients who are older, in those who achieve tight glycemic control, and during times of increased insulin sensitivity such as exercise and sleep.[36]

Nocturnal hypoglycemia is common in patients with type 1 diabetes and is usually asymptomatic.[37-38] Almost 50% of all episodes of severe hypoglycemia in patients with type 1 diabetes occur at night during sleep.[38] Nocturnal hypoglycemia can lead to disruption of sleep and delays in correction of the hypoglycemia.[1,38]

Symptoms and Signs

Hypoglycemia may cause adrenergic, cholinergic, and/or neuroglycopenic symptoms, although these can sometimes be nonspecific and relatively insensitive.[29,39,40] (*See Table 5.*)

Common signs of hypoglycemia include diaphoresis and pallor,[1] as well as slight elevations in heart rate and systolic blood pressure. Neuroglycopenic symptoms may include cognitive impairment, behavioral/personality changes, difficulties speaking, dizziness, blurred vision, weakness, incoordination, hemiplegia, seizures, and coma.[40,41] Neuroglycopenic manifestations are usually recognized by others.

These symptoms and signs can be mild, moderate, or severe, depending on how low the glucose falls and a variety of other factors. Manifestations of hypoglycemia may vary from person to person and can even vary within the same patient on different occasions.[42] Because the manifestations of hypoglycemia are nonspecific, many episodes go unrecognized. The patient may not notice any symptoms/signs of hypoglycemia, even though these are apparent to others. Older adults tend to have more neuroglycopenic manifestations compared with autonomic manifestations, and, thus, tend to have delayed recognition.[36]

Complications

Hypoglycemia often causes recurrent physical morbidity, recurrent or persistent psychosocial morbidity, or both in most patients with type 1 diabetes and many with type 2 diabetes.[43] In elderly patients with diabetes, even mild episodes of hypoglycemia may lead to adverse outcomes. The neuroglycopenic symptoms of hypoglycemia can increase the risk of falls and fractures.[44]

Because glucose is an obligate metabolic fuel for the brain, hypoglycemia can have potentially devastating effects on the brain.[11,29] Recurrent hypoglycemia has been associated with cognitive impairment in young children and elderly patients with diabetes, but the extent of these effects is unknown in other

age groups. Prolonged and profound hypoglycemia may result in permanent neurological damage and even brain death,[11] although these effects are rare.[45]

While rare, it is believed that diabetic hypoglycemia will cause sudden death.[45] In both type 1 and type 2 diabetes, the frequency of hypoglycemic episodes correlates with mortality.[2,3,23-25,43,45,46] Although the exact cause of mortality in these trials is not known, it is plausible that iatrogenic hypoglycemia may have resulted in cardiac arrhythmias, thus possibly contributing to an untimely death.[1] The "dead in bed syndrome," the unexpected death of a person that occurs while sleeping at night, is thought to be caused by a fatal ventricular arrhythmia.[1,47,48] It is believed that the sympathoadrenal response to hypoglycemia may cause a transiently prolonged QT interval and increased QT dispersion, resulting in a fatal arrhythmia.[1,47,48]

Risk Factors

Risk factors for hypoglycemia include insulin excess, decreased glucose availability, and defective counterregulatory responses.[1,2]

Insulin Excess: Absolute or relative insulin excess may occur in patients with diabetes.[1,2]

• Exogenous insulin and insulin secretagogues are the most common medications associated with hypoglycemia.[2,49] The prevalence of mild hypoglycemic symptoms has been reported in 30-50% of patients treated with insulin and 16-20% of patients treated with sulfonylureas.[49-52] Insulin secretagogues stimulate endogenous insulin secretion, suppress hepatic and renal glucose production, stimulate glucose utilization, and can cause hypoglycemia even in the setting of intact glycemic defenses if given in sufficient doses. Among the commonly used insulin secretagogues, those with a longer duration of action, such as glyburide, are associated with hypoglycemia more often.[49,53-55]

• Hypoglycemia occurs more frequently in patients treated with intensive hypoglycemic therapy,[56] and hypoglycemia is the most common adverse effect of intensive insulin therapy in both the hospital and outpatient settings.[1]

Table 5: Signs and Symptoms of Hypoglycemia

Adrenergic	Cholinergic	Neuroglycopenic
Palpitations	Sweating	Confusion
Anxiousness	Hunger	Decreased sharpness of senses
Tremors	Paresthesias	Behavior changes
Irritability		Lethargy
Pallor		Seizures
		Coma

Decreased Glucose Availability: This can occur from reduced intake or endogenous production.

• Decreased exogenous glucose intake, which may occur during an overnight fast, or with small, delayed, or missed meals, increases the potential for hypoglycemia.[2]

• Decreased endogenous glucose production may occur as a result of alcohol consumption or in patients with sepsis. Alcohol consumption is often the cause of, or a contributing factor to, hypoglycemia seen in patients who present to the ED.[57] Alcohol inhibits gluconeogenesis and can result in hepatic glycogen depletion and hypoglycemia, especially if there is limited food consumption.[1] Sepsis is a relatively common cause of hypoglycemia[1,58-61] and is likely due to cytokine-induced inhibition of gluconeogenesis in the setting of glycogen depletion, in addition to cytokine-accelerated glucose utilization.[59]

• Increased insulin-independent glucose utilization, such as from exercise-induced glucose utilization by muscle, can cause hypoglycemia in patients treated with insulin.[1,62] Even when plasma glucose levels are near normal or moderately elevated at the start of exercise, hypoglycemia can occur both during or shortly after exercise.[1,62]

• Increased sensitivity to insulin is often seen after weight loss, hours after exercise, following improved glycemic control, in the middle of the night, after withdrawal of glucocorticoid therapy,[1] and occasionally in patients with type 1 diabetes mellitus who develop adrenal insufficiency.[37,41] Among the latter patients, sensitivity to insulin is increased because of loss of the gluconeogenic effect of cortisol and the hyperglycemic effects of epinephrine.[34,51]

Decreased Clearance of Insulin:

• Decreased insulin clearance is commonly seen in patients with acute or chronic renal failure[1] who are treated with insulin or insulin secretagogues. Hypoglycemia in patients with chronic kidney disease may also be due to impaired gluconeogenesis and reduced renal glucose production.[1]

Defective Counter-Regulatory Responses:

• Insulin excess alone explains only a minority of episodes of hypoglycemia.[1,63] Impaired counter-regulatory response is the primary risk factor for subsequent hypoglycemia.[63] People with type 1 diabetes do not have the normal insulin and glucagon responses to hypoglycemia. As they experience recurrent hypoglycemia, the glycemic threshold becomes lower for the sympathoadrenal response to subsequent hypoglycemia, which leads to defective glucose counter-regulation.[5]

Diagnosis

The detection of hypoglycemia has been greatly facilitated by the development of reliable POC glucose testing devices. These devices are widespread, routinely carried by EMS vehicles, and extensively used in the ED, hospital, and physician offices. There are, however, technical aspects associated with the use of these devices that may provide false or markedly elevated values. If

the health care provider performing the test has even a small amount of sugar on his or her hands, as from a powdered-sugar pastry or donut, the test strip may become contaminated and report false elevated results.

Another potential problem with POC glucose testing is with the specimen source. In most settings where this test is used for rapid screening, the specimen source is capillary blood obtained by fingerstick using a lancet. A potential problem is that in critically ill patients, blood obtained by fingerstick (capillary source) tends to have higher glucose concentrations than that of arterial or venous samples.[64] Thus, hypoglycemia may go undetected in these critically ill patients.

Additional laboratory testing is guided by the clinical circumstance. Patients with a clearly defined precipitating circumstance (e.g., insulin-dependent diabetic who took his or her regular amount of prescribed insulin and then did not eat) do not require additional testing, especially if they respond as expected to treatment. However, for hypoglycemic ED patients who predominately presented for altered mental status, an observational study found that more than half of these patients had abnormalities on serum electrolytes or renal function.[65] Thus, it could be argued to have a low threshold for routine laboratory testing for such ED patients. Patients with hypoglycemia due to drug overdose or toxicity often have other blood chemistry abnormalities, and expanded testing is recommended.

For patients without diabetes who present with symptomatic hypoglycemia, a panel of tests obtained during the hypoglycemic episode is used to identify and classify potential causes. The panel includes measurement of plasma glucose, insulin level, c-peptide level, proinsulin level, beta-hydroxybutyrate, and a urine drug screen for oral hypoglycemic agents.[1] If possible, this specimen should be drawn before treatment.

Treatment

Patients with drug-treated diabetes should be instructed to undertake defensive actions when their plasma glucose concentration is < 70 mg/dL because of the concern of developing hypoglycemia.[8] Such actions include repeating the self-monitored blood glucose (SMBG) level to confirm hypoglycemia, consuming carbohydrates, and abstaining from tasks such as driving or operating heavy equipment while hypoglycemic.[8] (*See Table 6.*)

Most episodes of asymptomatic or mild-to-moderate symptomatic hypoglycemia are effectively self-treated by the consumption of carbohydrates. Plasma glucose concentration should be raised to the normal range. The "15-15 rule" can be used in the majority of cases in adults. This involves the ingestion of 15 g of fast-acting carbohydrates and a recheck of SMBG level 15 minutes later to ensure that the glucose level is > 70 mg/dL. If the glucose level is not above 70 mg/dL, the steps should be repeated until it is achieved.[66] Readily available items that contain 15 g of fast-acting carbohydrates include: 4 ounces of carbohydrate-containing juice or regular, non-diet soda; 8 ounces of milk; 3-4 glucose tablets; 1 tube of glucose gel; 5-6 hard candies; 2 tablespoons of raisins; 4 or 5 saltine crackers; 4 teaspoons of sugar; and 1 tablespoon of honey or corn syrup. Food that contains fat (like candy bars) or protein (cheese) should be avoided initially, since they slow the absorption of glucose.

In adults, 15-20 g of carbohydrates are usually sufficient to raise blood glucose to a safe range without causing hyperglycemia.[1,66] Clinical improvement should occur within 15-20 minutes of treatment.[67] Although most episodes of hypoglycemia are reversed once the glucose level is raised to the normal range, the glycemic response to oral glucose may be transient, especially in basal or intermediate insulin-induced hypoglycemia (often < 2 hours). Therefore, a long-acting carbohydrate with protein, such as a meal or more substantial snack, if the next meal is > 1 hour away, should be consumed shortly after the plasma glucose is raised to prevent recurrent symptoms.[1,66] It is also recommended that patients check their blood glucose levels serially after treatment with carbohydrates to ensure that they continue to remain within the euglycemic range, as individual responses may vary.[1] Rebound hypoglycemia is common due to ingestion of more carbohydrates than needed for the situation. Training patients and their families on a prompt but appropriate response to hypoglycemia may reduce this overshoot.

Patients treated with insulin or a secretagogue in combination with an alpha-glucosidase inhibitor should only consume pure glucose (dextrose) to treat symptomatic hypoglycemia. Alpha-glucosidase inhibitors slow the digestion of other carbohydrates, such as table sugar (sucrose), and, thus, consumption of non-dextrose carbohydrates will be less effective in raising blood sugar.

In cases of severe hypoglycemia occurring outside the hospital, when the patient is unconscious or is unable/unwilling to ingest carbohydrates, glucagon treatment is recommended.[1] Relatives and close friends should be trained to recognize the signs and symptoms of hypoglycemia and provide treatment should this complication occur. If hypoglycemia is suspected, a blood glucose level should be checked initially, especially if the patient is unconscious, to ensure that hyperglycemia is not the culprit. If this is not possible, then empiric treatment for hypoglycemia should be performed.[1]

Glucagon, injected subcutaneously or intramuscularly in a dose of 1 mg in adults, can be lifesaving in cases of severe hypoglycemia, especially if there is no intravenous access.[68] Glucagon rapidly counters the metabolic effects of insulin in the liver through stimulation of glycogenolysis and gluconeogenesis. Injected glucagon can raise blood glucose levels by 30-100 mg/dL within minutes and can lead to transient, but significant hyperglycemia.[1,68] Resolution of hypoglycemic symptoms with recovery of consciousness

usually occurs within 10 minutes after glucagon administration.[68] Rarely, nausea and vomiting may follow with this dose of glucagon. Therefore, the patient should be placed onto his or her side if unconscious to avoid the risk of aspiration. Once the patient is awake and able to tolerate oral food, he or she initially should consume a fast-acting carbohydrate and then a long-acting carbohydrate with protein, since glucagon depletes glycogen stores and potentially can lead to rebound hypoglycemia. If the patient remains unconscious 10 minutes after the glucagon injection, another injection should be given.

There are no efficacy data to guide the management of hypoglycemia outside the hospital if glucagon is not available prior to the arrival of emergency personnel. In the absence of other options, some experts suggest treatment with either glucose gel or cake frosting placed in the buccal mucosa or table sugar placed sublingually. Other experts do not recommend these options since there is no supporting evidence[69] and there also is a potential risk of aspiration. Hypothetically, an epinephrine injection will also raise the glucose but should only be used when other evidence-based treatments are not available.

In the ED and hospital, the standard parenteral therapy for hypoglycemia is intravenous glucose. The standard initial glucose dose for adults is 25 g of 50% glucose (D50) IV. This dose will typically raise serum glucose about 160 mg/dL, although the response is variable,[70] leading to the caution that serum glucose response cannot be reliably predicted after D50 administration. Usually, the glycemic response is only transient and, thus, a subsequent dose or glucose infusion often is required. It is recommended that patients ingest food with carbohydrates as soon as they are able to tolerate food by mouth.[1]

For patients under the influence of excess insulin activity, oral glucose ingestion may not be adequate to maintain blood glucose above 70 mg/dL. The reason is that one of the effects of insulin is to stimulate the incorporation of glucose delivered by the portal venous blood into hepatic glycogen, reducing the amount that can get through the liver and reach the systemic circulation. Thus, continued infusion of glucose is recommended to maintain blood glucose in cases of insulin or oral hypoglycemic overdose.[14,71-76] Similar to that seen with the variable response to D50, the response to glucose infusion is also variable. Typical glucose infusion rates reported to maintain euglycemia in insulin and sulfonylurea overdose are 100 to 200 mL/h of 10% glucose (D10),[77] although higher infusion rates may be necessary.[72,74,76]

Octreotide inhibits pancreatic insulin release and is used to treat hypoglycemia induced by sulfonylureas.[77,78] Published case reports have used doses of 50 to 100 micrograms IV or SC every 6 hours. Alternatively, an IV bolus of 50 micrograms followed by an infusion of 25 to 50 micrograms/h can be used.[79]

Table 6: Treatment of Hypoglycemia

Setting	Mild	Severe
Outpatient community	Oral glucose, "rule of 15"	Glucagon injection
Outpatient health care office	Oral glucose, "rule of 15"	Glucagon injection
Extended care facility	Oral glucose, "rule of 15"	Glucagon injection
Hospital	Oral glucose, "rule of 15"	IV glucose (dextrose)

Prevention

Frequent or severe hypoglycemia should lead to consideration of significantly changing the treatment regimen based on the review and application of the principles of aggressive glycemic therapy.[66] These principles include: patient self-management achieved through education and empowerment, ongoing professional guidance and support, frequent SMBG testing or continuous glucose sensing, flexible and individualized drug regimens, and individualized glycemic goals.[1]

Patient self-management can be improved through professional guidance and support, which is best provided by a chronic care model conducted by a diabetes care team.[80] Patients should be educated about the recognition and treatment of hypoglycemia.[81] They also should be informed that the typical hypoglycemic manifestations may be impaired after an episode of hypoglycemia, especially if severe. Frequent SMBG data can help detect glycemic variability and reduce the risk of hypoglycemia. This also means carrying testing supplies and items to treat hypoglycemia with them all of the time. ED discharge instructions after treatment for hypoglycemia should incorporate these recommendations.[81]

Treatment regimens should be flexible and individualized to minimize the risk of hypoglycemia. Among the insulin secretagogues, hypoglycemia is less common with glimepiride compared with glyburide.[53-55] Analog insulins have less hypoglycemia compared with NPH, regular, or premixed insulin.[82-84] Rapid-acting insulin analogs (Lispro, Aspart, Glulisine) reduce nocturnal hypoglycemia in patients with type 1 diabetes.[86] Long-acting insulin analogs (Glargine, Detemir) reduce nocturnal hypoglycemia and symptomatic hypoglycemia in patients with type 1 and type 2 diabetes.[82-84]

To date it appears insulin pump therapy does not reduce the hypoglycemia risk, as a recent systematic review of 15 randomized trials found no difference of mild, nocturnal, or severe hypoglycemia between continuous subcutaneous insulin infusion and multiple daily injection therapy with insulin analogs.[85] However, when the pump uses sensor-augmented continuous subcutaneous

Table 7: Hypoglycemia in Patients Without Diabetes

Well-appearing
• Accidental, surreptitious, or malicious use of hypoglycemic drugs
• Post-gastric bypass
• Insulinoma
• Functional beta-cell disorders (nesidioblastosis)
• Autoimmune hypoglycemia
• Reactive hypoglycemia
• Alimentary hypoglycemia
Ill-appearing
• Critical illness: sepsis, hepatic, renal or cardiac failure
• Cortisol deficiency
• Alcohol
Medication-induced
• Insulin
• Insulin secretagogues
• Cibenzoline, Gatifloxacin, Pentamidine, Quinine, Indomethacin, Glucagon (used during endoscopy)

insulin infusion, it has been shown to achieve lower A1C levels without an increase in hypoglycemia.[86]

Ultimately, glycemic goals should be individualized to match the health and life expectancy of the individual patient. Although intensive glycemic therapy has been shown to prevent or delay microvascular complications, including retinopathy, nephropathy, and neuropathy, the risk of hypoglycemia is also increased;[63,87-89] severe or frequent hypoglycemia is an absolute indication for setting less-aggressive glycemic goals. In addition, patients who are very young or old; patients who have multiple comorbidities, advanced microvascular or macrovascular complications; or patients with a limited life expectancy should have relaxed glucose goals that reduce the risk of hypoglycemia.[66]

Hypoglycemia in Patients Without Diabetes

Although hypoglycemia is a common event in persons with diabetes, it is a rare event in those healthy patients without diabetes because of the effectiveness of the key physiologic defenses in response to declining plasma glucose levels.[90] Hypoglycemia has become ensconced in the popular culture, and a variety of symptoms has been ascribed to it by the lay public. Only those non-diabetic individuals with documented Whipple's triad should undergo evaluation and management of hypoglycemia to avoid unnecessary workup and costs.[91]

Hypoglycemia in patients without diabetes can be categorized clinically based on whether the patient is well- or ill-appearing and/or treated with certain medications.[90] (*See Table 7.*) In those patients who are well-appearing, hypoglycemia usually is caused by either endogenous hyperinsulinism or accidental, surreptitious, or malicious administration of an insulin secretagogue or insulin.

Case reports have described patients who have developed hyperinsulinemic hypoglycemia after undergoing bariatric surgery. These cases can occur years after surgery and are difficult to treat. As there is an increasing number of people undergoing these procedures, this is an important potential complication of which to be aware.[92]

Drugs, including insulin, insulin secretagogues, alcohol, and others, are the most common cause of hypoglycemia, especially in the setting of critical illness or when enteral or parenteral nutrition is disrupted.[90] In patients who are ill-appearing and not receiving treatment with culprit medications, renal failure, hepatic failure, cardiac failure, sepsis, and inanition are the most common causes of hypoglycemia.[8,90] Although uncommon, hypoglycemia can occur in patients with cortisol or growth hormone deficiencies after prolonged fasting.[91] Fasting hypoglycemia also can occur rarely in patients with a non-islet cell tumor, which is typically a large mesenchymal or epithelial tumor (hepatomas, adrenocortical carcinomas, carcinoids) caused by the overproduction of an incompletely processed form of insulin-like growth factor II.[91]

Reactive hypoglycemia was first described in 1924.[93] This condition occurs in people who have a mismatch between insulin secretion and glucose absorption. Reactive hypoglycemia is defined as hypoglycemia that occurs within 4 hours of ingestion of food.[16] Patients who experience reactive hypoglycemia typically initially will experience mild, early post-meal hyperglycemia, and this will be followed with a vigorous insulin response with a greater than 75 mg/dL drop in glucose that overshoots the normal range and results in mild hypoglycemia. Although the recommended diagnostic workup is controversial,[94] many clinicians will utilize a 3- to 4-hour glucose tolerance test or results of the patient's mixed nutrient meal documentation. This condition often is considered a prediabetic condition. Reactive hypoglycemia is treated by small frequent meals with low carbohydrate content.

Alimentary hypoglycemia is an uncommon form of hypoglycemia.[95] This tends to occur in young, thin women who experience rapid transit through the gastrointestinal tract. This condition is very worrisome to the patient but rarely results in severe hypoglycemia. Further, it is not related to diabetes mellitus and does not predict an increased risk of diabetes mellitus in the future. This is more common in people with irritable bowel syndrome. Although not validated in controlled clinical trials, antispasmodic agents, such

as dicyclomine and hyoscyamine, appear to be helpful.

Summary

Hypoglycemia is a common and significant problem in diabetes; it is the rate-limiting factor for intensive glucose treatment. Hypoglycemia can be divided into mild, severe, asymptomatic, and relative hypoglycemia. The treatment of hypoglycemia varies based on its severity, cause, and location of treatment.

References

1. Cryer PE, et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2009;94:709-728.
2. Cryer PE. *Hypoglycemia in Diabetes. Pathophysiology, Prevalence and Prevention*. American Diabetes Association, Alexandria, VA, 2009.
3. Cryer PE. The barrier of hypoglycemia in diabetes. *Diabetes* 2008;57:3169-3176.
4. McCrimmon RJ, Sherwin RS. Hypoglycemia in type 1 diabetes. *Diabetes* 2010;59:2333-2339.
5. Whipple AO. The surgical therapy of hyperinsulinism. *J Int Chir* 1938;3:237-276.
6. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 2004;350:2272-2279.
7. Frier BM. Defining hypoglycaemia: What level has clinical relevance? *Diabetologia* 2009;52:31-34.
9. Amiel SA, et al. Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 1988;37:901-907.
8. Workgroup on Hypoglycemia, American Diabetes Association. Defining and reporting hypoglycemia in diabetes: A report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005;28:1245-1249.
10. Davis SN, et al. Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 1997;46:1328-1335.
11. Cryer PE. Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 2007;117:868-870.
12. Cryer PE. The prevention and correction of hypoglycemia. In: Jefferson L, et al, eds. *Handbook of Physiology*, Section 7. The Endocrine System. Volume II. The endocrine pancreas and regulation of metabolism. New York: Oxford University Press 2001;1057-1092.
13. A multicenter study of the accuracy of the One Touch Ultra home glucose meter in children with type 1 diabetes. The Diabetes Research in Children Network (DirecNet) Study Group. *Diabetes Technol Ther* 2003;5:933-941.
14. Carroll MF, Burge MR, Schade DS. Severe hypoglycemia in adults. *Rev Endocr Metab Disord* 2003;4:149-157.
15. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 2007;50:1140-1147.
16. Cryer P. 2008 Glucose homeostasis and hypoglycemia. In: Kronenberg H, eds. *Williams Textbook of Endocrinology*. 11th ed. Philadelphia: Saunders; 2007:1503-1533.
17. Donnelly LA, et al. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: A population-based study. *Diabet Med* 2005;22:749-755.
18. Farmer AJ, Brockbank KJ, Keech ML, et al. Incidence and costs of severe hypoglycemia requiring attendance by emergency medical services in South Central England. *Diabet Med* 2012 Mar 21 [Epub ahead of print]
19. KimJT, Oh TJ, Lee YA, et al. Increasing trend in the number of severe hypoglycemia patients in Korea. *Diabetes Metab J* 2011;35(2):166-172.
20. Simeone JC, Quilliam BJ. Predictors of emergency department and outpatient visits for hypoglycemia in type 2 diabetes: an analysis of a large US administrative claims database. *Ann Pharmacother* 2012;46(2):157-168.
21. Quilliam BJ, Simeone JC, Ozbay AB, Kogut SJ. The incidence and costs of hypoglycemia in type 2 diabetes. *Am J Manag Care* 2011;17(10):673-680.
22. UK Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease. UK Prospective Diabetes Study Group. *Diabetes* 1995;44:1249-1258.
23. Gerstein HC, et al. Effects of intensive glucose lowering in type 2 diabetes. The Action to Control Cardiovascular Risk in Diabetes Study Group. *N Engl J Med* 2008;358:2545-2559.
24. The ADVANCE Collaborative Group. Intensive blood control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560-2572.
25. Duckworth W, et al. Glucose control and vascular complications in veteran with type 2 diabetes. *N Engl J Med* 2009;360:129-139.
26. Ginde AA, Espinola JA, Camargo CA jr. Trends and disparities in US emergency department visits for hypoglycemia, 1993-2005. *Diabetes Care* 2008;31(3):511-513.
27. Gossell-Williams M, Williams-Johnson J, Francis L. Hypoglycaemic complications with diabetes mellitus management: the predominant adverse drug reaction presenting to the Accident and Emergency Department of The University Hospital of the West Indies. *West Indian Med J* 2010;59(5):555-560.
28. Curkendall SM, et al. Incidence and cost of hypoglycemia among patients with type 2 diabetes in the United States: Analysis of a health insurance database. *JCOM* 2011;18:455-462.
29. Cryer PE, et al. Hypoglycemia in diabetes. *Diabetes Care* 2003;26:1902-1912.
30. Dagogo-Jack SE, et al. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. *J Clin Invest* 1993;91:819-828.
31. Segel SA, et al. Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 2002;51:724-733.
32. Amiel SA, et al. Hypoglycemia in Type 2 diabetes. *Diabetic Med* 2008;25:245-254.
33. Cryer PE. Mechanisms of sympathoadrenal failure and autonomic failure and hypoglycemia in diabetes. *J Clin Invest* 2006;116:1470-1473.
34. Cryer PE. Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes* 2005;54:3592-3601.
35. White NH, et al. Identification of Type 1 diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 1983;308:485-491.
36. Spollett G. Type 2 diabetes across the lifespan. In: *The Art and Science of Diabetes Self-Management Education Desk Reference*. 2nd ed. Chicago, IL: American Association of Diabetes Educators; 2011.
37. Gold AE, et al. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 1994;17:697–703.
38. Allen KV, Frier BM. Nocturnal hypoglycemia: clinical manifestations and therapeutic strategies toward prevention. *Endocr Pract* 2003;9:530-543.
39. Towler DA, et al. Mechanism of awareness of hypoglycemia. Perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 1993;42:1791-1798.
40. Hepburn DA, et al. Symptoms of acute insulin-induced hypoglycemia in humans with and without IDDM. Factor-analysis approach. *Diabetes Care* 1991;14:949-957.
41. Cryer PE. Hypoglycemia. Chapter 339. In: *Harrison's Principles of Internal Medicine*. Fauci AS, et al. Vol 2, 17th ed. New York: McGraw Hill; 2008:1596-1607.
42. Cox DJ, et al. Perceived symptoms in the recognition of hypoglycemia. *Diabetes Care* 1993;16:519-527.
43. Cryer PE. Hypoglycaemia: The limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 2002;45:937-948.
44. Matyka K, et al. Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. *Diabetes Care* 1997;20:135-141.

45. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group; Jacobson AM, et al. Long-term effect of diabetes and its treatment on cognitive function. *N Engl J Med* 2007;356:1842-1852.

46. Skrivarhaug T, et al. Long-term mortality in a nationwide cohort of childhood onset type 1 diabetic patients in Norway. *Diabetologia* 2006;49:298-305.

47. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. *Diabet Med* 1991;8:49-58.

48. Lee SP, et al Influence of autonomic neuropathy on QTc interval lengthening during hypoglycemia in type 1 diabetes. *Diabetes* 2004;53:1535-1542.

49. White JR. The contribution of medications to hypoglycemia unawareness. *Diabetes Spectrum* 2007;20:77-80.

50. Cohen MR, et al. Survey of hospital systems and common serious medication errors. *J Healthc Risk Manag* 1998;18:16-27.

51. Fischer KF, et al. Hypoglycemia in hospitalized patients. Causes and outcomes. *N Engl J Med* 1986;315:1245-1250.

52. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: Pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 2005;28:2948-2961.

53. Gangji AS, et al. A systematic review and meta-analysis of hypoglycemia and cardiovascular events: a comparison of glyburide with other secretagogues and with insulin. *Diabetes Care* 2007;30:389-394.

54. Bolen S, et al. Systematic review: Comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. *Ann Intern Med* 2007;147:386-399.

55. Szoke E, et al. Effects of glimepiride and glyburide on glucose counterregulation and recovery from hypoglycemia. *Metabolism* 2006;55:78-83.

56. The Diabetes Control and Complications Trial Research Group. Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 1997;46:271-286.

57. Amiel S. Hypoglycemia in Patients with type 1 diabetes. In: Lebovits HD, ed. *Therapy for Diabetes and Related Disorders.* 5th Ed. Alexandria VA: American Diabetes Association; 2009: 372-375.

58. Miller SI, et al. Hypoglycemia as a manifestation of sepsis. *Am J Med* 1980;68:649-654.

59. Maitra SR, et al. Alterations in tissue glucose uptake during the hyperglycemic and hypoglycemic phases of sepsis. *Shock* 2000;13:379-385.

60. Henderson WR, Chittock DR, Dhingra VK, Ronco JJ. Hyperglycemia in acute ill emergency patients – cause or effect? *CJEM* 2006;8(5):339-343.

61. Tsai SH, Lin YY, Hsu CW, Cheng CS, Chu DM. Hypoglycemia revisited in the acute care setting. *Yonsei Med J* 2011;52(6):898-908.

62. Camacho RC, et al. Glucoregulation during and after exercise in health and insulin-dependent diabetes. *Exerc Sport Sci Rev* 2005;33:17–23.

63. Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. *Am J Med* 1991;90:450-459.

64. Mittadodla PS, Ahmad M. Beware of undetected hypoglycemia. *Emerg Med J* 2010;27(4):334.

65. Sinert R, Su M, Secko M, Zehtabchi S. The utility of routine laboratory testing in hypoglycemic emergency department patients. *Emerg Med J* 2009;26(1):28-31.

66. American Diabetes Association. Standards of medical care in diabetes—2011. *Diabetes Care* 2011;34(Suppl. 1):S11-S61.

67. Strote J, Simions R, Eisenberg M. Emergency medical technician treatment of hypoglycemia without transport. *Am J Emerg Med* 2008;26(3):291-295.

68. Vukmir RB, Paris PM, Yealy DM. Glucagon: Prehospital therapy for hypoglycemia. *Ann Emerg Med* 1991;20(4):375-379.

69. Gunning RR, Garber AJ. Bioactivity of instant glucose. Failure of absorption through oral mucosa. *JAMA* 1978;240:1611-1612.

70. Adler PM. Serum glucose changes after administration of 50% dextrose solution: Pre- and in-hospital calculations. *Am J Emerg Med* 1986;4(6):504-506.

71. Rowden AK, Fasano CJ. Emergency management of oral hypoglycemic drug toxicity. *Emerg Med Clin North Am* 2007;25(2):347-356.

72. Thewjitcharoen Y, Lekpittaya N, Himathongkam T. Attempted suicide by massive insulin injection: A case report and review of the literature. *J Med Assoc Thai* 2008;91(12):1920-1924.

73. Mork TA, Killeen CT, Patel NK, et al. Massive insulin overdose managed by monitoring daily insulin levels. *Am J Ther* 2011;18(5):e162-166.

74. Fasching P, Roden M, Stühlinger HG, et al. Estimated glucose requirement following massive insulin overdose in a patient with type 1 diabetes. *Diabet Med* 1994;11(3):323-325.

75. Shibutani Y, Ogawa C. Suicidal insulin overdose in a type 1 diabetic patient: Relation of serum insulin concentrations to the duration of hypoglycemia. *J Diabetes Complications* 2000;14(1):60-62.

76. Samuels MH, Eckel RH. Massive insulin overdose: Detailed studies of free insulin levels and glucose requirements. *J Toxicol Clin Toxicol* 1989;27(3):157-68.

77. Boyle PJ, et al. Octreotide reverses hyperinsulinemia and prevents hypoglycemia induced by sulfonylurea overdoses. *J Clin Endocrinol Metab* 1993;76:752-756.

78. Dougherty PP, Klein-Schwartz W. Octreotide's role in the management of sulfonylurea-induced hypoglycemia. *J Med Toxicol* 2010;6(2):199-206.

79. Soderstrom J, Murray L, Daly FF, et al. Toxicology case of the month: oral hypoglycaemic overdose. *Emerg Med J* 2006;23(7):565-567.

80. Warm EJ. Diabetes and the chronic care model: A review. *Curr Diabetes Rev* 2007;3:219-225.

81. Ginde AA, Pallian DJ, Camargo CA Jr. Hospitalization and discharge education of emergency department patients with hypoglycemia. *Diabetes Educ* 2008;34(4):683-691.

82. Gough SC. A review of human and analogue insulin trials. *Diabetes Res Clin Pract* 2007;77:1-15.

83. Hirsch IB. Insulin analogues. *N Engl J Med* 2005;352:174-183.

84. Gough K, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007:CD005613.

85. Fatourechi M, et al. Hypoglycemia with intensive insulin therapy: A systematic review and meta-analysis of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metab* 2008;94:729-740.

86. Bergenstal RM, et al. Effectiveness of a sensor-augmented insulin pump therapy in type 1 diabetes. *N Engl J Med* 2010;363:311-320.

87. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986.

88. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;52:837-53.

89. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;52:854-865.

90. Cryer PE. Glucose homeostasis and hypoglycemia. In: Kronenberg HM, et al., eds. *Williams Textbook of Endocrinology.* 11th ed. Philadelphia, PA: Elsevier Health Sciences; 2008: 1503-1533.

91. Fletcher AA, Campbell WR. The blood sugar following insulin administration and the symptom complex: Hypoglycemia. *J Metab Res* 1922;2:637-649.

92. Amiel S. Hypoglycemia in patients with type 1 diabetes. In: *Therapy for Diabetes and Related Disorders.* 5th ed. Alexandria VA: American Diabetes Association; 2009: 372-375.

93. Harris S. Hyperinsulinemia and Dysinsulinism. *JAMA* 1924;83:729-733.

94. Brun JF, et al. Postprandial reactive hypoglycemia. *Diabetes Metab* 2000;26:337-351.

95. Leichter SB. Alimentary hypoglycemia: A new appraisal. *Am J Clin Nutr* 1979;32:2104-2113.

Physician CME Questions

1. According to the American Diabetes Association Workgroup on Hypoglycemia, what hypoglycemia level should be addressed for patients with drug-treated diabetes?
   A. when the self-monitored blood glucose level is < 70 mg/dL (3.9 mmol/L)
   B. when the self-monitored blood glucose level is < 63 mg/dL (3.5 mmol/L)
   C. when the self-monitored blood glucose level is < 55 mg/dL (3.0 mmol/L)
   D. when their self-monitored blood glucose level is < 40 mg/dL (2.2 mmol/L)

2. Which of the following is *not* a critical physiological mechanism involved in preventing hypoglycemia?
   A. an increase in cortisol secretion
   B. a reduction in insulin secretion
   C. a reduction in growth hormone secretion
   D. an increase in epinephrine secretion

3. Which of the following is *not* an adrenergic symptom of hypoglycemia?
   A. anxiety
   B. tremor
   C. palpitations
   D. paresthesias

4. Which of the following medications has the strongest strength of evidence for causing hypoglycemia?
   A. trimethoprim-sulfamethoxazole
   B. pentamidine
   C. levofloxacin
   D. ACE inhibitors

5. Endogenous glucose production is decreased in which of the following situations?
   A. alcohol consumption
   B. exercise
   C. acute renal failure
   D. withdrawal from steroid treatment

6. Which of the statements regarding insulin secretagogues is *false*?
   A. They stimulate insulin secretion.
   B. They suppress hepatic glucose production.
   C. They stimulate glucose utilization.
   D. The do not cause hypoglycemia.

7. Consumption of which of the following is *not* effective self-treatment for an episode of mild symptomatic hypoglycemia?
   A. 1/2 cup of juice
   B. 1 tablespoon of honey
   C. 1 oz. of cheese
   D. 4 saltine crackers

8. Which of the following medications is used standardly for the treatment of hypoglycemia in the hospital setting?
   A. dextrose IV
   B. epinephrine SQ
   C. octreotide IV
   D. glucagon IM

9. Which is the recommended dose of glucagon to treat hypoglycemia?
   A. 1 mg SC
   B. 5 mg IM
   C. 10 mg IV
   D. 25 mg IV

10. Octreotide is used to treat hypoglycemia caused by which drug or toxin?
    A. alcohol
    B. sulfonylureas
    C. metformin
    D. insulin

CME Objectives

Upon completion of this educational activity, participants should be able to:

- recognize specific conditions in patients presenting to the emergency department;
- apply state-of-the-art diagnostic and therapeutic techniques to patients with the particular medical problems discussed in the publication;
- discuss the differential diagnosis of the particular medical problems discussed in the publication;
- explain both the likely and rare complications that may be associated with the particular medical problems discussed in the publication.

CME Instructions

HERE ARE THE STEPS YOU NEED TO TAKE TO EARN CREDIT FOR THIS ACTIVITY:

1. Read and study the activity, using the provided references for further research.

2. Log on to **www.cmecity.com** to take a post-test; tests can be taken after each issue or collectively at the end of the semester. *First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice, or renewal notice.*

3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.

5. **Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.** You will no longer have to wait to receive your credit letter.

Emergency Medicine Reports™ (ISSN 0746-2506) is published biweekly by AHC Media, a division of Thompson Media Group LLC, 3525 Piedmont Road, N.E., Six Piedmont Center, Suite 400, Atlanta, GA 30305. Telephone: (800) 688-2421 or (404) 262-7436.

Senior Vice President/Group Publisher: Donald R. Johnston

Executive Editor: Shelly Morrow Mark

Managing Editor: Leslie Hamlin

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Emergency Medicine Reports, P.O. Box 105109, Atlanta, GA 30348.

Back issues: $31. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $359 each; 10 to 20 additional copies, $319 each.

Subscriber Information

Customer Service: 1-800-688-2421

Customer Service E-Mail:
customerservice@ahcmedia.com

Editorial E-Mail:
shelly.mark@ahcmedia.com

World Wide Web page:
http://www.ahcmedia.com

Subscription Prices

1 year *with* 60 ACEP/65 AMA/39 AAFP Category 1/Prescribed credits: $544

1 year *without* credit: $399
Add $17.95 for shipping & handling

Resident's rate $199

Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

All prices U.S. only.
U.S. possessions and Canada, add $30 plus applicable GST. Other international orders, add $30.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *65 AMA PRA Category 1 Credits™*. Each issue has been designated for a maximum of 2.50 *AMA PRA Category 1 Credits™*. Physicians should claim only credit commensurate with the extent of their participation in the activity.

Approved by the American College of Emergency Physicians for 60 hours of ACEP Category 1 credit.

This Enduring Material activity, *Emergency Medicine Reports*, has been reviewed and is acceptable for up to 39 Prescribed credit(s) by the American Academy of Family Physicians. AAFP accreditation begins January 1, 2012. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1.50 Prescribed credits. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Please forward your comments on the quality of this activity to cmecomment@aafp.org.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman. Opinions expressed are not necessarily those of this publication. Mention of products or services does not constitute endorsement. Clinical, legal, tax, and other comments are offered for general guidance only; professional counsel should be sought for specific situations.

This CME activity is intended for emergency and family physicians. It is in effect for 24 months from the date of the publication.

Emergency Medicine Reports
The Practical Journal for Emergency Physicians

Hypoglycemia in Adults

Types of Hypoglycemia

Type of Hypoglycemia	Glucose Level	Etiology	Related to Diabetes or Other Disease
Mild asymptomatic	< 70 mg/dL but > 50 mg/dL	Many	Sometimes related
Mild symptomatic	< 70 mg/dL but > 50 mg/dL	Many	Sometimes related
Severe hypoglycemia	< 50 mg/dL or any low glucose that requires assistance from others	Hypoglycemic agents or excessive insulin secretion	Yes
Probable hypoglycemia	Not measured	Many	Likely related
Relative hypoglycemia	> 70 mg/dL	Likely in patient with diabetes on treatment	Yes, both type 1 and type 2
Reactive hypoglycemia	Initial rise above normal after meal, followed by a 75 mg/dL drop	Altered insulin secretion — usually first phase insulin secretory defect	Can occur in prediabetics
Post-absorptive hypoglycemia	Typically drops after meals without prior rise	Altered GI transit	No — diabetes Yes — bowel disorders

Pathophysiologic Classification of Hypoglycemia in Adults

Mechanism	Drug or Toxin	During Fasting	Postprandial
Increased insulin activity	Excess insulin Sulfonylureas Cibenzoline* Gatifloxacin* Pentamidine* Quinine* Indomethacin*	Insulinoma Functional beta-cell disorders Antibodies to insulin receptor or insulin	Post GI surgery Alimentary
Liver dysfunction	Ethanol Non-selective beta-blockers	Septic shock Heart failure Multi-endocrine deficiency	Ackee fruit
Decreased substrate	Chronic renal insufficiency	Uremia Large tumors Severe wasting	
Increased glucose consumption		Prolonged exercise	

* Drugs with moderate quality of evidence for causing hypoglycemia

Physiologic Response to Hypoglycemia

Glucose Level	Response	Result
80-85 mg/dL	Suppression of insulin secretion	Primary defense against hypoglycemia
65-70 mg/dL	Increased glucagon secretion Increased cortisol and growth hormone secretion	Primary counter-regulatory response Slower counter-regulatory response, minor role
50-55 mg/dL	Hunger	Increase in exogenous glucose
< 50 mg/dL	Neuroglycopenic symptoms	Compromised response

Response to Hypoglycemia: Normal vs. Diabetics

Condition	Insulin	Glucagon	Epinephrine
Normal	Sharply decreases	Increases	Increases
Early type 2 diabetes	Decreases	Increases	Increases
Late type 2 diabetes	No decrease	No increase	Attenuated increase
Type 1 diabetes	No decrease	No increase	Attenuated increase

Signs and Symptoms of Hypoglycemia

Adrenergic	Cholinergic	Neuroglycopenic
Palpitations Anxiousness Tremors Irritability Pallor	Sweating Hunger Paresthesias	Confusion Decreased sharpness of senses Behavior changes Lethargy Seizures Coma

Treatment of Hypoglycemia

Setting	Mild	Severe
Outpatient community	Oral glucose, "rule of 15"	Glucagon injection
Outpatient health care office	Oral glucose, "rule of 15"	Glucagon injection
Extended care facility	Oral glucose, "rule of 15"	Glucagon injection
Hospital	Oral glucose, "rule of 15"	IV glucose (dextrose)

Hypoglycemia in Patients Without Diabetes

Well-appearing

- Accidental, surreptitious, or malicious use of hypoglycemic drugs
- Post-gastric bypass
- Insulinoma
- Functional beta-cell disorders (nesidioblastosis)
- Autoimmune hypoglycemia
- Reactive hypoglycemia
- Alimentary hypoglycemia

Ill-appearing

- Critical illness: sepsis, hepatic, renal or cardiac failure
- Cortisol deficiency
- Alcohol

Medication-induced

- Insulin
- Insulin secretagogues
- Cibenzoline, Gatifloxacin, Pentamidine, Quinine, Indomethacin, Glucagon (used during endoscopy)

Supplement to *Emergency Medicine Reports*, May 21, 2012: "Hypoglycemia in Adults." *Authors:* **Cara O'Shaughnessey, DO**, Diabetes Fellow, Ohio University Heritage College of Osteopathic Medicine, O'Bleness Health System, Athens, OH; and **Jay H. Shubrook, Jr., DO, FACOFP, FAAFP**, Associate Professor of Family Medicine and Director of Diabetes Fellowship, Ohio University Hertiage College of Osteopathic Medicine, Athens, OH.