

Hypoglycemia in Type 1 and Type 2 Diabetes: Physiology, Pathophysiology, and Management

Vanessa J. Briscoe, PhD, and Stephen N. Davis, MD

Hypoglycemia is one of the most feared complications of diabetes treatment. Unfortunately, the threat and incidence of iatrogenic hypoglycemia is increased in attempts to achieve euglycemia as recommended by current treatment guidelines. These recommendations are based on results from two landmark studies, the Diabetes Control and Complications Trial (DCCT) and U.K. Prospective Diabetes Study (UKPDS), which demonstrated the benefits of intensive glycemic control in type 1 and type 2 diabetes, respectively.^{1,2} These studies proved that microvascular and some macrovascular complications could be reduced by rigorous metabolic control. However, the associated increased frequency of hypoglycemia has limited the clinical implementation of such intensive therapy because of the pharmacokinetic imperfections of available treatment regimens.³⁻⁵

Hypoglycemia commonly occurs in clinical practice. Approximately 90% of all patients who receive insulin have experienced hypoglycemic episodes.⁶ Nonetheless, the combination of understanding the physiological counterregulatory responses induced by hypoglycemia and monitoring glycemic therapy can help reduce the prevalence of iatrogenic hypoglycemia.³⁻¹⁰

Prevalence of Hypoglycemia in Diabetes

Surveys investigating the prevalence of hypoglycemia have provided some alarming results. The DCCT reported a threefold increase in severe hypoglycemia and coma in intensively treated

patients versus conventionally treated patients.¹¹ An intensively treated individual with type 1 diabetes can experience up to 10 episodes of symptomatic hypoglycemia per week and severe temporarily disabling hypoglycemia at least once a year.^{1,11,12} An estimated 2–4% of deaths of people with type 1 diabetes have been attributed to hypoglycemia.⁴ Hypoglycemia is also relatively common in type 2 diabetes, with prevalence rates of 70–80% in clinical trials using insulin to achieve good metabolic control.²

Donnelly et al.¹³ randomly surveyed individuals ($n = 267$) with type 1 diabetes and insulin-treated type 2 diabetes to prospectively record hypoglycemic events encountered over a 4-week period. Of the 267 subjects, 155 reported 572 incidents of hypoglycemia. The type 1 diabetic subjects reported a rate of 43 events per patient per year, whereas subjects with type 2 diabetes reported a rate of 16 events per patient per year. For individuals with type 1 diabetes, predictors of hypoglycemia included a history of previous hypoglycemia ($P = 0.006$).

IN BRIEF

The threat and incidence of hypoglycemia is the major limiting factor in intensive glycemic control for both type 1 and type 2 diabetes. This article reviews the physiology of the normal counterregulatory responses to hypoglycemia and the deficient counterregulatory defenses that occur in patients with diabetes. Treatment paradigms for establishing good glycemic control while limiting hypoglycemia are also discussed.

Predictors for hypoglycemia for the insulin-treated type 2 diabetic subjects included a history of previous hypoglycemia ($P < 0.0001$) and duration of insulin treatment ($P = 0.014$). Self-reports of severe hypoglycemia in type 2 diabetic subjects were lower than in type 1 diabetic subjects. The authors also concluded that hypoglycemia occurs more often than previously reported² in insulin-treated type 2 diabetes and with sufficient frequency to cause significant morbidity.

Clinical Impact of Iatrogenic Hypoglycemia

The brain depends on a continual supply of glucose and is vulnerable to any glucose deprivation.^{5,8,9} Unable to synthesize or store this primary source of energy, the brain is one of the first organs affected by lowered blood glucose levels.^{5,8,9} Once plasma glucose concentrations fall below the physiological range at a glycemic threshold of ~ 70 mg/dl,⁵ a sequence of responses is activated that includes release of neuroendocrine hormones (also called counterregulatory or anti-insulin hormones), stimulation of the autonomic nervous system (ANS), and production of neurogenic and neuroglycopenic symptoms to protect the brain and limit systematic effects of hypoglycemia.

The normal physiological counterregulatory response to hypoglycemia consists of suppression of insulin release and secretion of glucagon and pancreatic polypeptide from the pancreas, epinephrine from the adrenal medullae, norepinephrine from sympathetic postganglionic nerve terminals and adrenal

medulla, cortisol from the adrenal cortex, and growth hormone from the anterior pituitary gland.⁷ In humans, inhibition of insulin secretion is the initial defense against falling glucose and occurs at a plasma glucose concentration of ~ 80 mg/dl.

Glucagon and epinephrine are the primary fast-acting hormones in the defense against acute hypoglycemia. Glucagon acts to increase endogenous glucose production and does so via increases in hepatic glycogenolysis and gluconeogenesis, providing three carbon glucose substrates (lactate, pyruvate, alanine, and glycerol). Epinephrine can also acutely increase endogenous glucose production. Epinephrine has effects similar to glucagon on hepatic glucose production but can also stimulate net renal glucose production. Additionally, epinephrine has an important physiological function in reducing insulin-stimulated glucose uptake.

During the prolonged hypoglycemia that is usually observed in clinical practice, it is the reduced glucose uptake in peripheral tissues that contributes most to the preservation of circulating glucose levels and hence the defense against hypoglycemia. Activation of the sympathetic nervous system (via both circulating catecholamines and direct innervation) results in increased lipolysis in adipocytes. The increased release of free fatty acids (FFAs) results in significant glucose sparing (because tissues can oxidize FFAs instead of glucose). In fact, the contribution of FFAs has been estimated to be 25% of the total defense against hypoglycemia.³⁻⁷

Growth hormone and cortisol play a modest role in the metabolic defense against acute hypoglycemia but become more important during prolonged hypoglycemia.⁷ In fact, the counterregulatory actions of growth hormone and cortisol on increasing glucose production and restraining glucose disposal do not become evident until 4 hours after the onset of hypoglycemia. Even so, their counterregulatory actions are only ~ 20% compared to that of epinephrine.⁷

Symptoms of Hypoglycemia

For people with type 1 diabetes and many with advanced type 2 diabetes, hypoglycemia is a fact of life.¹⁻⁵ Those attempting to achieve better glycemic control suffer many episodes of mild to moderate hypoglycemia. Although the level of plasma glucose that indicates hypoglycemia is sometimes debated, it may be best defined in a physiological context as a plasma glucose of < 70 mg/dl (< 60 mg/dl whole blood). This is because the glycemic threshold for activation of the anti-insulin neuroendocrine counterregulatory response occurs at a plasma glucose of 70 mg/dl. Additionally, antecedent hypoglycemia of 70 mg/dl has been demonstrated to reduce counterregulatory responses to subsequent hypoglycemia.³⁻⁷

Symptoms of hypoglycemia are divided into two categories. Neurogenic (autonomic) symptoms are triggered by a falling glucose level and cause patients to recognize that they are experiencing a hypoglycemic episode.^{5,7,8} These symptoms are activated by the ANS and are mediated in part by sympathoadrenal release of catecholamines (norepinephrine and epinephrine) from the adrenal medullae and acetylcholine from post-synaptic sympathetic nerve endings.^{5,8} Neurogenic symptoms and signs associated with elevated epinephrine levels

include shakiness, anxiety, nervousness, palpitations, sweating, dry mouth, pallor, and pupil dilation.^{4,5,9} The cholinergic-mediated symptoms include diaphoresis, hunger, and paresthesias.³⁻⁵ However, it should be noted that epinephrine infusion in the presence of euglycemia to achieve levels commonly seen during hypoglycemia only produces 20% of the total neurogenic symptom scores found during hypoglycemia. This indicates that the genesis of hypoglycemic symptoms is multifocal and is probably mainly generated from central nervous system (CNS) efferent pathways.¹⁴

Neuroglycopenic symptoms occur as a result of brain neuronal glucose deprivation.^{3-5,9,10} Evidence of neuroglycopenia can be the signal most often recognized by patients' family and friends. These symptoms include abnormal mentation, irritability, confusion, difficulty speaking, ataxia, paresthesias, headaches, stupor, and eventually (if untreated) seizures, coma, and even death.^{3-5,9} Neuroglycopenic symptoms can also include transient focal neurological deficits (e.g., diplopia, hemiparesis)³⁻⁵ (Table 1).

Hypoglycemia and Glycemic Thresholds

The glycemic thresholds responsible for the activation of the physiological

Table 1. Symptoms of Hypoglycemia

Neurogenic (ANS) Symptoms (Caused by Falling Glucose Level)	Neuroglycopenic Symptoms (Caused by Brain Neuronal Glucose Deprivation)
Shakiness	Abnormal mentation
Trembling	Irritability
Anxiety	Confusion
Nervousness	Difficulty in thinking
Palpitations	Difficulty speaking
Clamminess	Ataxia
Sweating	Paresthesias
Dry mouth	Headaches
Hunger	Stupor
Pallor	Seizures
Pupil dilation	Coma
	Death (if untreated)

defenses against hypoglycemia are dynamic rather than static.⁷ Thus, patients with a higher hemoglobin A_{1c} (A1C) may perceive symptoms of hypoglycemia at a higher plasma glucose level than those with more intensive control.⁸ In fact, these patients may generate hypoglycemic symptoms even when their plasma glucose is above the normal range. This phenomenon is called “relative hypoglycemia” and is associated with release of counterregulatory hormones. This phenomenon commonly occurs when patients undergo intensification of their glucose control. This syndrome is self-limiting and usually takes 2–4 weeks for the brain to readjust to the improved and thus relatively reduced circulating glucose levels.^{8–10,15,16}

The opposite is true in intensively controlled individuals with diabetes. They may not recognize hypoglycemia until their plasma glucose is considerably lower than the normal physiological glycemic thresholds.^{5,10} The changes in glycemic thresholds can be caused acutely by antecedent hypoglycemia and chronically by persistent hyperglycemia.^{1–5}

To test the hypothesis that hypoglycemia itself causes reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia, Heller and Cryer¹⁷ measured counterregulatory responses during repeated hypoglycemic clamp studies. These seminal experiments determined that two episodes of antecedent moderate hypoglycemia (50 mg/dl) resulted in significant reductions of plasma epinephrine, glucagon, pancreatic polypeptide, and cortisol responses to next-day hypoglycemia. Neurogenic and neuroglycopenic symptom responses were also reduced after antecedent hypoglycemia. A later study¹⁸ investigated the effects of morning hypoglycemia on neuroendocrine and metabolic responses to subsequent afternoon hypoglycemia. These experiments demonstrated that only one episode of prolonged, moderate hypoglycemia can also produce substantial blunting of counterregulatory hormones and the

symptomatic response to subsequent hypoglycemia.¹⁸

The above studies combined with conceptually similar results from differing laboratories allowed the term “hypoglycemia-associated autonomic failure” to be coined. This syndrome includes reduced neuroendocrine counterregulatory responses to hypoglycemia and lowered glycemic thresholds for activation of physiological defenses against hypoglycemia, which together lead to a condition of hypoglycemic unawareness. Glycemic thresholds are shifted to lower plasma glucose levels in intensively treated type 1 and type 2 diabetic individuals,^{10,18–21} which further limits efforts to attain euglycemia.^{3,4}

Counterregulatory Hormone Responses to Hypoglycemia in Older Adults

The risk of severe or fatal hypoglycemia associated with the use of oral hypoglycemic agents and insulin increases exponentially with age.^{22,23} Also, older adults with comorbidities, those using multiple medications, and those who are frequently hospitalized are at greater risk for iatrogenic hypoglycemia.²⁴ Most people with type 2 diabetes are > 60 years of age.⁸ Therefore, it is important to appreciate the idiosyncratic and age-specific manifestations of hypoglycemic symptoms.⁹

Meneilly et al.²² have investigated the effects of age on counterregulatory responses during clamped hypoglycemia. Older adults with type 2 diabetes demonstrated reduced glucagon and growth hormone responses but increased epinephrine and cortisol responses when compared to age-matched nondiabetic control subjects. However, hypoglycemic symptom scores were similar in both groups at all levels of glycemia.

Matyka et al.,²⁵ on the other hand, found differences in hypoglycemic symptom responses when comparing healthy older men aged 60–70 years with younger men aged 22–26 years. During hyperinsulinemic-hypoglycemic

clamp studies, neuroendocrine responses for the two groups were similar. However, symptoms began earlier in the younger men and were more intense. Measures of psychomotor coordination deteriorated earlier in the older subjects and to a greater degree. The usual 10–20 mg/dl plasma glucose difference between the subjective awareness of hypoglycemia and the onset of cognitive dysfunction was lost in the older men.

This altered counterregulatory effect may contribute to the altered cognitive response to reductions in blood glucose. Thus, the lower glycemic threshold to hypoglycemia in older people may limit the time available to self-treat and thereby increase the risk of developing incapacitating neuroglycopenia.^{22,25} Additionally, these neurological symptoms of hypoglycemia may be misinterpreted in older patients because of coexisting illnesses, such as cerebrovascular diseases or dementia.^{22,25}

Counterregulatory Hormone Responses to Hypoglycemia in Women

There is a large sexual dimorphism in counterregulatory responses to hypoglycemia. It has been clearly demonstrated that both healthy young women and women with type 1 diabetes have reduced neuroendocrine, ANS, and metabolic (endogenous glucose production) counterregulatory responses compared to age- and BMI-matched men.^{26–30}

This is not because of differences in glycemic thresholds for activation of counterregulatory responses. In a series of separate glucose clamps at glycemic targets of 90, 70, 60, and 50 mg/dl, Davis et al.²⁹ demonstrated that reduced CNS drive is responsible for the sexual dimorphic responses to hypoglycemia occurring in women. In a subsequent study, Sandoval et al.³⁰ determined that estrogen is the mechanism responsible for this sexual dimorphism.

Despite this, the prevalence of hypoglycemic episodes in type 1 diabetes is similar for men and women.¹ This apparent paradox may be explained by the fact

that women may be more resistant than men to the blunting effects of antecedent hypoglycemia on the ANS.³⁰ Thus, two episodes of antecedent hypoglycemia in men will cause a twofold greater blunting of counterregulatory responses to subsequent hypoglycemia compared to women, with the result being that the usual sexual dimorphic response to hypoglycemia is eliminated.

Exercise-Related Hypoglycemia

Hypoglycemia can occur during, 1–2 hours after, or up to 17 hours after exercise. The mechanisms responsible for this phenomenon have been the subject of recent work.⁷ Aerobic exercise results in an increase in both insulin- and non-insulin-mediated glucose uptake.

During moderate-intensity exercise in nondiabetic individuals, endogenous insulin secretion is reduced by 40–60%. Thus, reductions are recommended in replacement insulin doses during exercise (basal and/or prandial insulin). This can be supplemented with oral intake of 10–20 g of carbohydrate every 30–60 minutes depending on the intensity of exercise. Insulin sensitivity increases ~ 2 hours after moderate-intensity exercise. Thus, consideration should be given to reducing basal and/or prandial insulin doses for 24 hours after exercise.

Additionally, recent studies have demonstrated that there is a vicious cycle of counterregulatory failure between exercise and hypoglycemia.⁷ Thus, two episodes of prolonged, moderate-intensity exercise can reduce ANS and neuroendocrine responses by 50% during subsequent hypoglycemia. Similarly, two episodes of antecedent hypoglycemia can reduce counterregulatory responses during subsequent exercise by 40–50%.⁷ Therefore, individuals who have had a previous episode of hypoglycemia are at greater risk of hypoglycemia during exercise. This may be countered by temporarily increasing glycemic targets, reducing preexercise insulin, and consuming appropriate amounts of carbohydrate.

Mechanisms of Counterregulatory Responses to Hypoglycemia in Type 1 Diabetes

Epinephrine (not glucagon) is the main defense against hypoglycemia in patients with type 1 diabetes of > 5 years' duration. This is because the pancreatic α -cell glucagon secretory response to hypoglycemia is irreversibly lost.^{3–6}

Unfortunately, epinephrine responses to hypoglycemia also become impaired in type 1 diabetic patients undergoing intensive insulin treatment. This places intensively treated type 1 diabetic patients at a significant risk for recurrent hypoglycemia.^{31,32} These frequent bouts of hypoglycemia further reduce the counterregulatory responses to future hypoglycemia by $\geq 50\%$. This creates a vicious cycle of iatrogenic hypoglycemia-associated autonomic failure, whereby hypoglycemia induces further hypoglycemia.^{3–5,31}

Davis et al.³³ demonstrated that the magnitude of antecedent hypoglycemia produced proportional blunting of counterregulatory responses to subsequent hypoglycemia. In other words, the greater the depth of antecedent hypoglycemia, the greater the magnitude of subsequent counterregulatory failure.

The ANS is exquisitely sensitive to the effects of antecedent hypoglycemia. Two episodes of hypoglycemia of only 70 mg/dl can blunt subsequent counterregulatory responses by ~ 30% in men. Similarly, short durations (20 minutes) of antecedent hypoglycemia also produce significant blunting of subsequent counterregulatory responses.³³ The reduction in ANS counterregulatory responses has significant clinical consequences because type 1 diabetic patients with deficient glucagon and epinephrine responses to hypoglycemia have a ≥ 25 -fold risk of hypoglycemia during intensive insulin therapy.¹

Hypoglycemia-associated autonomic failure is an acutely acquired syndrome that should be differentiated from classical diabetic autonomic neuropathy.^{3–6,19,31} It is also possible that patients with

hypoglycemia-associated autonomic failure also have reduced adrenergic sensitivity (i.e., tissue responsiveness to circulating epinephrine). Korytkowski et al.³⁴ demonstrated that type 1 diabetic subjects with blunted counterregulatory responses to hypoglycemia had reduced β -adrenergic sensitivity compared to patients with normal counterregulatory responses to hypoglycemia and healthy control subjects. Aftab-Guy et al.¹⁴ also demonstrated that patients with type 1 diabetes had reduced whole-body tissue sensitivity to epinephrine, which was exacerbated by intensive glycemic control. This reduced tissue sensitivity to epinephrine resulted in lower endogenous glucose production and less inhibition of insulin-stimulated glucose uptake. The above data may be interpreted to indicate that reduced tissue responsiveness to epinephrine is an additional contributor to the syndrome of hypoglycemia-associated autonomic failure.

Fritsche et al.³⁵ demonstrated that if hypoglycemic episodes are avoided for 4 months, β -adrenergic sensitivity and hypoglycemic symptom responses increase, despite a persistently blunted epinephrine response to hypoglycemia. This may indicate that increases in β -adrenergic sensitivity are a prelude to restoration of endocrine and autonomic function when hypoglycemic episodes are avoided.⁷ Although controversial, other studies have also reported that some or all of the features of hypoglycemia-associated autonomic failure (i.e., blunted neuroendocrine counterregulatory responses) can be reversed with strict avoidance of antecedent hypoglycemia.^{3–5,36–38}

Mechanisms of Counterregulatory Responses to Hypoglycemia in Type 2 Diabetes

Type 2 diabetes is a heterogeneous disease affecting a range of individuals from children to older adults. Therapies include diet, oral medications, glucagon-like peptide-1 analogs, insulin, or combination therapies and vary depending on patients' progressive β -cell failure.³⁹

Hence, the clinical effect of hypoglycemia-associated autonomic failure in type 2 diabetes is less well established,³⁻⁵ and results differ considerably with respect to age, comorbidity, treatment modality (diet versus oral hypoglycemic agents versus insulin), metabolic control, body fat composition, and the presence of diabetic neuropathies.^{39,40}

However, Segel et al.⁴⁰ tested the hypothesis that there are neuroendocrine changes in glycemic responses to hypoglycemia in individuals with advanced type 2 diabetes. They reported that the glucagon response to falling plasma glucose was virtually absent in advanced insulin-treated type 2 diabetes. Glycemic thresholds for autonomic and symptomatic responses to hypoglycemia were also shifted to lower glucose concentrations by recent antecedent hypoglycemia.

Hence, patients with advanced type 2 diabetes, like those with type 1 diabetes, are at risk for hypoglycemia-associated autonomic failure and the resultant vicious cycle of recurrent iatrogenic hypoglycemia.^{31,40}

Reducing the Risk of Iatrogenic Hypoglycemia

Fear of hypoglycemia is the major concern of patients receiving endogenous or exogenous insulin replacement therapy. Furthermore, patients receiving intensive insulin therapy have about a threefold greater incidence of severe disabling hypoglycemia than those receiving conventional insulin therapy.^{1,41}

Education regarding all aspects of diabetes care is important in the prevention and treatment of hypoglycemia. Carbohydrate counting, insulin and oral medication dosing, concomitant medications, alcohol intake, exercise, and even driving should be included in the discussion. Education will help alleviate fear of hypoglycemia that may impede ideal glycemic control.⁴² Reducing iatrogenic hypoglycemia will involve patient empowerment and anticipatory guidance by both patients and health care providers. Providers will also take on the

role of facilitator as they help patients navigate through the maze of diabetes self-care.

The topic of hypoglycemia has priority and demands to be routinely addressed with patients receiving medications that may themselves or in combination cause hypoglycemia. Lack of understanding of the diabetes-related therapeutic regimen will contribute to repeated incidents of hypoglycemia.⁴²⁻⁴⁷ Patients must understand time action profiles of their diabetes medications and realize that excessive treatment can be harmful. Providers should urge patients to wear potentially lifesaving diabetes alert identification.

Blood glucose monitoring is fundamentally important for people who experience hypoglycemic episodes, especially before they perform critical tasks such as driving.^{41,42} Also, in older individuals with diabetes who have comorbidities such as dementia, cerebral vascular accident, or depression, consideration should be given to these confounding factors.⁴⁸ Factors that may predispose such patients to hypoglycemia include increased polypharmacy or medication nonadherence, impaired renal or hepatic metabolism, and poor or erratic nutrition.^{22,23,41,42} Hence, the American Geriatrics Society has recommended an A1C of $\leq 7\%$ for healthy older adults and an A1C of $\leq 8\%$ for the frail elderly.⁴⁸

If patients report a history of hypoglycemia, details regarding the time of episodes need to be identified and the treatment regimen adjusted accordingly (Table 2). If these events go without intervention, the risk of recurrent severe hypoglycemia is high.⁴⁵

Injected insulin can produce absolute or relative insulin excess largely because of dosing and pharmacokinetics.⁴² With a basal-bolus insulin regimen, morning fasting hypoglycemia implicates the long- or intermediate-acting insulin. Daytime hypoglycemia may be caused by the rapid-, short-, or longer-acting insulins, depending on the regimen. Nocturnal hypoglycemia may also be caused by regular and longer-acting

Table 2. Hypoglycemia Risk Factors

- Missed or delayed meal
- Eating less food at a meal than planned
- Vigorous exercise without carbohydrate compensation
- Taking too much diabetes medicine (e.g., insulin, insulin secretagogues, and meglitinides)
- Drinking alcohol

insulin. Substitution of preprandial regular insulin with rapid-acting insulin (e.g., glulisine, lispro, or aspart) reduces the frequency of daytime hypoglycemia.^{43,44} Similarly, substitution of a long-acting insulin analog (e.g., glargine or detemir) for intermediate-acting insulins such as NPH, lente, or premix 70/30 or 50/50 also reduces the frequency of nocturnal and daytime hypoglycemia.⁴⁴

Insulin pump therapy (continuous subcutaneous insulin infusion) that uses rapid-acting insulin analogs can cause both nocturnal and morning fasting hypoglycemia. With nocturnal hypoglycemia, the basal insulin infusion rate may be problematic, whereas with fasting or daytime hypoglycemia, the preprandial insulin bolus doses, the basal insulin infusion rate, or both may be causing the problem.⁴⁴

Insulin secretagogues—sulfonylureas, repaglinide, and nateglinide—can also produce hypoglycemia related to absolute or relative insulin excess. However, the sulfonylureas may pose the greatest risk of hypoglycemia in patients with altered renal or hepatic function and in older adults.⁴² Hence, agents such as glimepiride, glipizide XL, or nateglinide that are shorter-acting and have glucose-dependent insulin secretion would be preferable to reduce hypoglycemic risks.⁴²

Hypoglycemia unawareness (loss of warning symptoms of hypoglycemia) implies recurrent hypoglycemia.⁴² Assessment of frequency and severity of hypoglycemia is required at each clinic visit. Additionally, inquiring at what

blood glucose level patients can first sense low plasma glucose will provide an assessment of hypoglycemia unawareness.

If there is still no apparent cause from the history or blood glucose log, patients may be experiencing hypoglycemia during the night.^{41,42} Indeed, nighttime hypoglycemia can be a common occurrence in people with type 1 diabetes.^{1,45} Sleep can preclude detection of symptoms warning of impending hypoglycemia.^{41,42} Approaches to the problem of nocturnal hypoglycemia include insulin regimen adjustments, such as the use of rapid-acting rather than regular insulin during the day and a long-acting basal insulin. Administration of bedtime snacks may be also appropriate.^{41,42,45}

If a diagnosis of hypoglycemic unawareness is made, the solution will involve the acceptance of somewhat higher glucose levels in the short term. At least a 3-week period of meticulous avoidance of hypoglycemia could be attempted with the goal of encouraging a return to awareness of hypoglycemia.¹⁻⁵ With the return of symptomatic hypoglycemia, patients can once more work toward achieving better glycemic control.

Review of patients' self-monitoring of blood glucose log will help interpret blood glucose patterns. Patients should always have a rapidly available source of glucose with them to treat hypoglycemia at the first sign of a low glucose (Table 3). Hypoglycemia (plasma glucose < 70 mg/dl), including asymptomatic hypoglycemia and most episodes of mild to moderate symptomatic hypoglycemia, is effectively self-treated by ingestion of some form of glucose. Pure glucose is preferred, although any form of carbohydrate that contains glucose will raise plasma glucose.

The "rule of 15" is a helpful treatment regimen when patients are able to self-treat. Typically, 15 g of carbohydrate (rapidly absorbing forms of glucose such as glucose gel, sugar-containing soda, or glucose tablets) should

Table 3. Tips for Preventing Hypoglycemia

- If blood glucose is < 70 mg/dl, give 15–20 g of quick-acting carbohydrate (1–2 teaspoons of sugar or honey, 1/2 cup of regular soda, 5–6 pieces of hard candy, glucose gel or tablets as directed, or 1 cup of milk).
- Test blood glucose 15 minutes after treatment. If it is still < 70 mg/dl, re-treat with 15 g of additional carbohydrate.
- If blood glucose is not < 70 mg/dl but it is > 1 hour until the next meal, have a snack with starch and protein (crackers and peanut butter, crackers and cheese, half of a sandwich, or crackers and a cup of milk).
- Keep glucagon injection kit available for patients who are unconscious or unable to take in oral carbohydrate. Instruct family members and caregivers about how to safely administer glucagon. Emergency glucagon kits are available with prescription only.

raise the blood glucose by 50 mg/dl in ~ 15 minutes. The glycemic response to oral glucose is transient; therefore, ingestion of a small complex carbohydrate snack shortly after the plasma glucose concentration rises is generally advisable, especially if the next meal is longer than 1 hour away.

Hypoglycemic patients who are unconscious or unable because of neuroglycopenia to take in oral carbohydrates can be treated with a parental glucagon injection. Glucagon kits require a prescription. Glucagon acts by mobilizing glucose stores from the liver via glycogenolysis. Thus, it is less effective in glycogen-depleted states (e.g., prolonged starvation or alcohol ingestion).

It is important that a glucagon kit be available for use and that patients' family members or caregivers are knowledgeable in its use. One does not need to be a health care professional to administer glucagon. Instruction regarding the potential side effects of glucagon (i.e., vomiting) is important. This will prevent any surprise and subsequent hesitancy to use it in the future. Also, care should be taken to ensure that the kit has not expired.

Intravenous glucose is the preferable treatment of severe iatrogenic hypoglycemia, particularly that caused by a sulfonylurea. These reactions are more likely to occur in elderly patients and are often prolonged and require

continuous glucose infusion and frequent feedings.^{41,42}

Conclusions

The threat and incidence of iatrogenic hypoglycemia is a major limiting factor in intensive glycemic management of diabetes. Nonetheless, it is possible to both improve glycemic control and minimize hypoglycemic risks by understanding the physiological counterregulatory responses and aggressively monitoring glycemic therapy.

Hypoglycemia is problematic in type 1 diabetes during aggressive glycemic therapy and in advanced type 2 diabetes because of compromised glucose counterregulatory systems. Therefore, education concerning self-monitoring of blood glucose, diet, physiological insulin replacement, medication, and lifestyle are important to maintain good glycemic control, avoid hypoglycemia, and prevent long-term complications.

REFERENCES

- ¹The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complication in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
- ²The U.K. Prospective Diabetes Study Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complication in patients with type 2 diabetes. *Lancet* 352:837–853, 1998
- ³Cryer PE: Hypoglycemia risk reduction in type 1 diabetes. *Exp Clin Endocrinol Diabetes* 109:S412–S423, 2001

- ⁴Cryer PE: Current concepts: Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med* 350:2272–2279, 2004
- ⁵Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 26:1902–1912, 2003
- ⁶Cryer PE: *Hypoglycemia: Pathophysiology, Diagnosis, and Treatment*. New York, Oxford University Press, 1997
- ⁷Diedrich L, Sandoval D, Davis SN: Hypoglycemia associated autonomic failure. *Clin Auton Res* 12:358–365, 2002
- ⁸Zammit NN, Frier BM: Hypoglycemia in type 2 diabetes. *Diabetes Care* 28:2948–2961, 2005
- ⁹McAuley V, Deary IJ, Freier BM: Symptoms of hypoglycemia in people with diabetes. *Diabet Med* 18:690–705, 2001
- ¹⁰Amiel SA, Sherwin RS, Simonson DC, Tamborlane WV: Effect of intensive insulin therapy on glycemic thresholds for counterregulatory hormone release. *Diabetes* 37:901–907, 1988
- ¹¹The DCCT Research Group: Hypoglycemia in the Diabetes Control and Complications Trial. *Diabetes* 46:271–286, 1997
- ¹²Hepburn DA, MacLeod KM, Pell AC, Scougal IJ, Frier BM: Frequency and symptoms of hypoglycaemia experienced by patients with type 2 diabetes treated with insulin. *Diabet Med* 10:231–237, 1993
- ¹³Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese P: Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 22:749–755, 2005
- ¹⁴Aftab-Guy D, Sandoval D, Richardson MA, Tate D, Davis SN: Effects of glycemic control on target organ responses to epinephrine in type 1 diabetes. *Am J Physiol Endocrinol Metab* 289:E258–E265, 2005
- ¹⁵Korzon-Burakowska A, Hopkins D, Matyka K, Lomas J, Pernet A, Macdonald I, Amiel S: Effects of glycemic control on protective responses against hypoglycemia in type 2 diabetes. *Diabetes Care* 21:283–290, 1998
- ¹⁶Boyle PJ, Schwartz NS, Shah SD, Clutter WE, Cryer PE: Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. *N Engl J Med* 318:1487–1492, 1988
- ¹⁷Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 4:223–226, 1991
- ¹⁸Davis SN, Tate D: Effects of morning hypoglycemia on neuroendocrine and metabolic responses to subsequent afternoon hypoglycemia in normal man. *J Clin Endocrinol Metab* 86:2043–2050, 2001
- ¹⁹Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. *J Clin Invest* 91:819–828, 1993
- ²⁰Segel SA, Paramore DS, Cryer PE: Defective glucose counterregulation in type 2 diabetes (Abstract). *Diabetes* 49: A131, 2000
- ²¹Spyer G, Hattersley AT, MacDonald IA, Amiel S, MacLeod KM: Hypoglycaemic counterregulation at normal blood glucose concentrations in patients with well controlled type 2 diabetes. *Lancet* 356:1970–1974, 2000
- ²²Meneilly GS, Cheung E, Tuokko H: Altered responses to hypoglycemia of healthy elderly people. *Diabetes* 43:403–410, 1994
- ²³Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM: Perceived symptoms of hypoglycaemia in elderly type 2 diabetic patients treated with insulin. *Diabet Med* 15:398–401, 1998
- ²⁴Shorr RI, Ray WA, Daugherty JR, Griffin MR: Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 157:1681–1686, 1997
- ²⁵Matyka K, Evans M, Lomas J, Cranston I, MacDonald I, Amiel SA: Altered hierarchy of protective responses against severe hypoglycemia in normal aging in healthy men. *Diabetes Care* 20:135–141, 1997
- ²⁶Amiel SA, Maran A, Powrie JK, Umpleby AM, MacDonald IA: Gender differences in counterregulation to hypoglycemia. *Diabetologia* 36:460–464, 1993
- ²⁷Davis SN, Goldstein RE, Price L, Jacobs J, Cherrington AD: The effects of insulin on the counterregulatory response to equivalent hypoglycemia in patients with insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 77:1300–1307, 1993
- ²⁸Diamond MP, Jones T, Caprio S, Hallarman L, Diamond MC, Addabbo M, Tamborlane WV, Sherwin RS: Gender influences counterregulatory hormone responses to hypoglycemia. *Metabolism* 42:1568–1572, 1993
- ²⁹Davis SN, Fowler S, Costa F: Hypoglycemic counterregulatory responses differ between men and women with type 1 diabetes. *Diabetes* 49:65–72, 2000
- ³⁰Sandoval DA, Ertl AC, Richardson MA, Tate DB, Davis SN: Estrogen blunts neuroendocrine and metabolic responses to hypoglycemia. *Diabetes* 52:1749–1755, 2003
- ³¹Cryer PE: Mechanisms of hypoglycemia-associated autonomic failure and its component syndromes in diabetes. *Diabetes* 54:3592–3598, 2005
- ³²White NH, Skor A, Cryer PE, Levandoski L, Dier DM, Santiago JV: Identification of type 1 diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 308:485–491, 1993
- ³³Davis SN, Shavers C, Mosqueda-Garcia R, Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 46:1328–1335, 1997
- ³⁴Korytkowski MT, Mookan M, Veneman TE, Mitrakou A, Cryer PE, Gerich JE: Reduced beta-adrenergic sensitivity in patients with type 1 diabetes and hypoglycemia unawareness. *Diabetes Care* 21:1939–1943, 1998
- ³⁵Fritsche A, Stefan N, Haring H, Gerich J, Stumvoll M: Avoidance of hypoglycemia restores hypoglycemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. *Ann Intern Med* 134:729–736, 2001
- ³⁶Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA: Restoration of hypoglycemia awareness in patients with long-duration insulin-dependent diabetes. *Lancet* 344:283–287, 1994
- ³⁷Fanelli C, Pampanelli S, Epifano L, Rabbotti AM, Ciofetta M, Modarelli F, DiVincenzo A, Annibale B, Lepore M, Lalli C, Sindaco P, Brunetti P, Bolli G: Relative roles of insulin and hypoglycemia on induction of neuroendocrine responses to, symptoms of, and deterioration of cognitive function in hypoglycemia in male and female humans. *Diabetologia* 37:797–807, 1994
- ³⁸Dagogo-Jack S, Rattarasarn C, Cryer PE: Reversal of hypoglycemia unawareness, but not defective glucose counterregulation, in IDDM. *Diabetes* 43:1426–1434, 1994
- ³⁹de Galan BE, Hoekstra JBL: Glucose counterregulation in type 2 diabetes mellitus. *Diabet Med* 18:519–527, 2001
- ⁴⁰Segel SA, Paramore DS, Cryer PE: Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 51:724–732, 2002
- ⁴¹The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complication trial. *Am J Med* 90:450–459, 1991
- ⁴²Gabrieli I, Shamoon H: Hypoglycemia in diabetes: common, often unrecognized. *Cleveland Clin J Med* 71:335–342, 2004
- ⁴³Cryer PE, Childs BP: Negotiating the barrier of hypoglycemia in diabetes. *Diabetes Spectrum* 15:20–27, 2002
- ⁴⁴Heller SR, Amiel SA, Mansell P: Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. *Diabetes Care* 22:1607–1611, 1999
- ⁴⁵Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA: Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. *Diabetes Care* 23:639–643, 2000
- ⁴⁶Muhlhaue I, Overmann H, Bender R, Bott U, Berger M: Risk factors of severe hypoglycemia in adult patients with type 1 diabetes—a prospective population based study. *Diabetologia* 41:1274–1282, 1998
- ⁴⁷Perriello G, DeFeo P, Torlone E, Fanelli C, Santeusano F, Brunetti P, Bolli GB: The dawn phenomenon in type 1 (insulin-dependent) diabetes mellitus: magnitude, frequency, variability, and dependency on glucose counterregulation and insulin sensitivity. *Diabetologia* 34:21–28, 1991
- ⁴⁸Wright EE: Treat to target: ABCs for the elderly. *DOC News* 3:4, 2006

Vanessa J. Briscoe, PhD, is a clinical research nurse practitioner, and Stephen N. Davis, MD, is chief of the Division of Diabetes, Endocrinology and Metabolism and Rudolph Kampmeier Professor of Medicine and Molecular Physiology and Biophysics at the Vanderbilt School of Medicine in Nashville, Tenn.