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.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).

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 reported 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,9 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 systemic 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. 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.5-7

Growth hormone and cortisol play a modest role in the metabolic defense against acute hypoglycemia but become more important during prolonged hypoglycemia. 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. 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.2-7

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 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.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.3-5,8,9 Evidence of neuroglycopenia can be the signal most often recognized by patients’ family and friends. These symptoms include abnormal mentation, irritability, confusion, difficulty speaking, ataxias, 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>
<thead>
<tr>
<th>Table 1. Symptoms of Hypoglycemia</th>
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<tr>
<td><strong>Neurogenic (ANS) Symptoms</strong> (Caused by Falling Glucose Level)</td>
</tr>
<tr>
<td>Shakiness</td>
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<tr>
<td>Trembling</td>
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<tr>
<td>Anxiety</td>
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<td>Nervousness</td>
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<td>Clamminess</td>
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<tr>
<td>Sweating</td>
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<tr>
<td>Dry mouth</td>
</tr>
<tr>
<td>Hunger</td>
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<tr>
<td>Pallor</td>
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<td>Pupil dilation</td>
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defenses against hypoglycemia are
dynamic rather than static.7 Thus,
patients with a higher hemoglobin A1c
(A1C) may perceive symptoms of hypo-
glycemia at a higher plasma glucose
level than those with more intensive con-
trol.8 In fact, these patients may generate
hypoglycemic symptoms even when
their plasma glucose is above the normal
range. This phenomenon is called “rela-
tive hypoglycemia” and is associated
with release of counterregulatory hor-
mones. This phenomenon commonly
occurs when patients undergo intensifi-
cation of their glucose control. This syn-
drome is self-limiting and usually takes
2–4 weeks for the brain to readjust to the
improved and thus relatively reduced cir-
culating 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 consid-
ably lower than the normal physiologi-
cal glycemic thresholds.5,10 The
changes in glycemic thresholds can be
caused acutely by antecedent hypo-
glycemia and chronically by persistent
hyperglycemia.1–5

To test the hypothesis that hypo-
glycemia itself causes reduced neuroen-
docrine and symptomatic responses to
subsequent hypoglycemia, Heller and
Cryer17 measured counterregulatory
responses to hypoglycemia and lowered
glycemic thresholds for activation of
physiological defenses against hypo-
glycemia, which together lead to a con-
dition of hypoglycemic unawareness.
Glycemic thresholds are shifted to lower
plasma glucose levels in intensively
treated type 1 and type 2 diabetic indi-
viduals,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 hypo-
glycemic 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.5 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 hypo-
glycemia. Older adults with type 2 dia-
betes 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.,21 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. Howev-
er, 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
can 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 there-
by increase the risk of developing inca-
pacitating neuroglycopenia.22,25 Addition-
ally, these neurological symptoms of
hypoglycemia may be misinterpreted in
older patients because of coexisting ill-
nesses, 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 hypo-
glycemia. It has been clearly demonstrat-
ed that both healthy young women and
women with type 1 diabetes have
reduced neuroendocrine, ANS, and meta-
bolic (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 hypo-
glycemic episodes in type 1 diabetes is
similar for men and women.1 This appar-
ent 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.\textsuperscript{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.\textsuperscript{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 preprandial 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 \(\sim 2\) 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.\textsuperscript{7} Thus, two episodes of antecedent hypoglycemia 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\%.\textsuperscript{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 \(\geq 5\) years’ duration. This is because the pancreatic \(\alpha\)-cell glucagon secretory response to hypoglycemia is irreversibly lost.\textsuperscript{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.\textsuperscript{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.\textsuperscript{3–5,31}

Davis et al.\textsuperscript{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 \(\sim 30\%\) in men. Similarly, short durations (20 minutes) of antecedent hypoglycemia also produce significant blunting of subsequent counterregulatory responses.\textsuperscript{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 \(\geq 25\)-fold risk of hypoglycemia during intensive insulin therapy.\textsuperscript{1}

Hypoglycemia-associated autonomic failure is an acutely acquired syndrome that should be differentiated from classical diabetic autonomic neuropathy.\textsuperscript{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.\textsuperscript{34} demonstrated that type 1 diabetic subjects with blunted counterregulatory responses to hypoglycemia had reduced \(\beta\)-adrenergic sensitivity compared to patients with normal counterregulatory responses to hypoglycemia and healthy control subjects. Aftab-Guy et al.\textsuperscript{14} also demonstrated that patients with type 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.\textsuperscript{35} demonstrated that if hypoglycemic episodes are avoided for 4 months, \(\beta\)-adrenergic sensitivity and hypoglycemic symptom responses increase, despite a persistently blunted epinephrine response to hypoglycemia. This may indicate that increases in \(\beta\)-adrenergic sensitivity are a prelude to restoration of endocrine and autonomic function when hypoglycemic episodes are avoided.\textsuperscript{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.\textsuperscript{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 \(\beta\)-cell failure.\textsuperscript{39}
Hence, the clinical effect of hypoglycemia-associated autonomic failure in type 2 diabetes is less well established, 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.

However, Segel et al. 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.

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.

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. 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.

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. 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.

Factors that may predispose such patients to hypoglycemia include increased polypharmacy or medication nonadherence, impaired renal or hepatic metabolism, and poor or erratic nutrition.

Hence, the American Geriatrics Society has recommended an A1C of ≤ 7% for healthy older adults and an A1C of ≤ 8% for the frail elderly.

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.

Injected insulin can produce absolute or relative insulin excess largely because of dosing and pharmacokinetics. 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 insulin. Substitution of preprandial regular insulin with rapid-acting insulin (e.g., glulisine, lispro, or aspart) reduces the frequency of daytime hypoglycemia.

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.

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.

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. Hence, agents such as gliemperide, glipizide XL, or nateglinide that are shorter-acting and have glucose-dependent insulin secretion would be preferable to reduce hypoglycemic risks.

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

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**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
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. Indeed, nighttime hypoglycemia can be a common occurrence in people with type 1 diabetes. Sleep can preclude detection of symptoms warning of impending hypoglycemia. 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.

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. 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 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. Instruct 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 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.

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


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.


Wright EE: Treat to target: ABCs for the elderly. *DOC News* 3:4, 2006

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