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Hypoglycemia in diabetes: Common, often unrecognized

■ ABSTRACT

Hypoglycemic episodes in patients with diabetes often go unrecognized, and over time, patients may lose the ability to sense hypoglycemia, increasing their risk. Intensive diabetes control is beneficial for patients with diabetes, but it increases their risk of hypoglycemia, underscoring the complexity of diabetes management.

■ KEY POINTS

Epinephrine release during hypoglycemia becomes progressively defective in type 1 diabetes. This decrease in epinephrine response is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of impaired awareness of hypoglycemia (ie, lack of the warning symptoms of prevailing hypoglycemia).

At every visit, one should probe for details of episodes that the patient recognized as being caused by hypoglycemia, but also assess whether the patient has experienced events that went unrecognized.

Although most episodes of nocturnal hypoglycemia are asymptomatic, some patients complain of sleep disturbances (vivid dreams or nightmares), morning headache (feeling hungover), chronic fatigue, or mood changes (mainly depression).

HYPOGLYCEMIA poses a major barrier to diabetes treatment. On one hand, we want to maintain tight glycemic control to prevent the vascular complications of diabetes, but we also have to ensure the safety and comfort of the patient by avoiding hypoglycemia—and by recognizing and treating it if it occurs.

Hypoglycemic events are probably common, especially in patients with type 1 diabetes. And when patients with type 2 diabetes receive insulin, they may become more prone to hypoglycemic episodes. Unfortunately, the more episodes of hypoglycemia a patient has, the more the body's response is blunted, decreasing the patient's awareness of an episode.

Thus, we need to be vigilant in monitoring patients for increasing episodes of hypoglycemia, and for events that a patient may not realize were caused by hypoglycemia.

■ CONSEQUENCES OF HYPOGLYCEMIA

Hypoglycemia can cause severe morbidity and sometimes death, usually depending on its severity or duration. Thus, it may be associated with a spectrum of symptoms progressing from autonomic activation to behavioral changes to altered cognitive function to seizures or coma (the latter observed only when blood glucose levels are < 30 mg/dL or with prolonged hypoglycemia).

Furthermore, owing to patients' (and sometimes physicians') fear of hypoglycemia, intensive diabetes treatment may be relaxed, which ultimately results in inferior glycemic control. Other immediate and long-term consequences of hypoglycemia are its impact on various activities of daily living such as driving, employment, and even home life.

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■ INSULIN EXCESS, OTHER FACTORS

Insulin excess—due either to endogenous secretion or to exogenous doses—appears to be the most consistent cause of hypoglycemia, and iatrogenic hypoglycemia is the most common scenario.¹ However, other factors such as dietary intake, physical activity, alcohol use, and drug interactions also may increase the risk of hypoglycemia.^{2–4}

In addition, studies over the last 2 decades strongly suggest that deficits in glucose counterregulation are important—and perhaps dominant—factors in the development of severe hypoglycemia.⁵

■ HOW COMMON IS HYPOGLYCEMIA?

Recent clinical trials have better quantified the risk of hypoglycemia—in particular, severe hypoglycemia—in both type 1 and type 2 diabetes.^{6–8}

Severe hypoglycemia is operationally defined as an episode that the patient cannot self-treat, so that external help is required, regardless of the blood glucose concentration or whether the patient experiences seizures or loss of consciousness.

Mild or moderate hypoglycemia refers to episodes that the patient can self-treat, regardless of the severity of symptoms, or when blood glucose levels are noted to be lower than 60 mg/dL.

The incidence of mild or moderate hypoglycemic episodes is difficult to determine accurately because they are rarely reported, although they are common in insulin-treated patients. Furthermore, diabetic patients with hypoglycemia-associated autonomic failure (see below) might not be aware of such events.

Episodes of severe hypoglycemia are better documented, although the incidence was different in different studies, likely owing to differences in the populations studied (eg, levels of glycemic control, intensity of insulin treatment, diabetes education).

In type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) reported 62 severe hypoglycemic episodes per 100 patient-years.⁶ The true risk may be higher in clinical practice, however, because patients at high risk for severe hypoglycemia were excluded

from this study. And indeed, population-based studies in northern Europe reported 100 to 160 episodes of severe hypoglycemia per 100 patient-years,^{7,8} even though glycemic control may not have been as close to normal in these studies as in the DCCT.

In type 2 diabetes, severe hypoglycemia appears to be much less common, but when patients with type 2 diabetes receive insulin they may become as susceptible to hypoglycemia as patients with type 1 diabetes. Leese et al⁸ reported the following incidence rates of severe hypoglycemia (episodes per 100 patient-years):

- In patients with type 1 diabetes—11.5
- In patients with type 2 diabetes treated with insulin—11.8
- In patients with type 2 diabetes treated with oral hypoglycemic drugs—0.05.

Since recent studies also demonstrated that improved glycemic control prevents or delays microvascular complications (neuropathy, retinopathy, and nephropathy) and perhaps macrovascular complications (heart attacks, peripheral vascular disease, strokes) in both type 1 and type 2 diabetes, the clinical decision to pursue such treatment goals in the face of possible iatrogenic hypoglycemia must be made on a case-by-case basis.

■ THE NORMAL RESPONSE

Counterregulatory responses to hypoglycemia have been studied extensively in experiments in humans by infusing insulin to reduce the plasma glucose concentration.⁹

A decrease in plasma glucose normally triggers a cascade of reactions, mostly hormonal, that rapidly return the glucose concentration to baseline levels. Ultimately there is an increase in glucose production in the liver and kidneys and a decrease in peripheral glucose utilization (mainly in muscle and fat tissue). Both mechanisms act in opposition to the effects of insulin and, hence, result in the reversal of hypoglycemia.^{9–11}

Different counterregulatory mechanisms are activated at different threshold levels of glucose concentration.⁹

A decrease in endogenous insulin secretion is the first defense against a falling plasma glucose concentration. This mechanism is

Insulin excess appears to be the most consistent cause of hypoglycemia



critical in patients with residual endogenous insulin secretion. In normal beta cells, insulin secretion is suppressed at a plasma glucose threshold of about 83 mg/dL.¹²

Of the other hormones, **epinephrine** and **glucagon** appear to be the most potent counterregulatory factors. These hormones are secreted promptly after plasma glucose levels fall, and both induce a rapid increase in endogenous glucose production. The glycemic thresholds for secretion of these hormones is normally about 68 mg/dL.

Epinephrine and glucagon appear to have similar quantitative effects on endogenous glucose production; hence, a deficient response of either hormone alone does not impair glucose counterregulation.^{12–14} For example, most patients with recent-onset type 1 diabetes secrete less glucagon during hypoglycemia than people without diabetes, but they can still secrete enough epinephrine to mount an appropriate response.

Other major counterregulatory hormones seem to be less critical in the initial 30 to 60 minutes of a hypoglycemic episode but are important in the later stage of glucose stabilization.¹² **Cortisol** and **growth hormone** both help the liver to sustain glucose output in the face of hyperinsulinemia. In addition, these hormones reduce peripheral glucose use during recovery from hypoglycemia, an action shared by epinephrine.¹¹

■ SYMPTOMS VARY GREATLY

Symptoms of hypoglycemia vary greatly among patients and depend on the individual's sensitivity.

In mild hypoglycemia, symptoms result from an autonomic nervous system response in concert with the hormonal counterregulatory responses.¹⁵ These symptoms include tremor, perspiration, palpitations, irritability, nervousness, headache, hunger, tachycardia, and pallor,^{13,15} and they subside once plasma glucose is restored to normal levels.

A further decrease in plasma glucose induces neuroglycopenic symptoms (ie, due to depletion of glucose in the central nervous system) such as difficulty in concentration, slurred speech, blurred vision, drop in body temperature, and behavioral changes.¹⁵

■ HOW DO PATIENTS KNOW WHEN GLUCOSE IS LOW?

Most patients recognize the early warning signs of hypoglycemia in time to take countermeasures. The lack of such symptoms despite hypoglycemia is termed *impaired awareness of hypoglycemia*, a syndrome linked to defective counterregulation in patients with diabetes.

Role of the brain

Accumulating evidence suggests that the brain—in particular, the ventromedial hypothalamus (VMH)—plays an important role in glucose sensing.

In dogs, the counterregulatory response to peripheral hypoglycemia can be abolished by infusing glucose directly into the brain.¹⁶ In rats, the counterregulatory response can also be abolished by selectively destroying the VMH or infusing concentrated glucose solutions into the ventromedial nuclei.^{17,18} Conversely, selective glycopenia in the cells within the VMH activates counterregulation, even if the peripheral blood glucose concentration is normal.¹⁹

Role of the liver

In parallel, various lines of evidence suggest that the liver—in particular, the portohepatic vascular system—may play a role in sensing blood glucose concentrations and activating the counterregulatory response to hypoglycemia.²⁰

Experimentally, if the glucose concentration in the portal vein is normalized during systemic hypoglycemia, the sympathoadrenal response is markedly suppressed. In addition, destruction of afferent nerves in the portal vein in dogs blunts the catecholamine response during hypoglycemia.²¹

Together, these studies suggest that glycemic sensors for hypoglycemia may be localized both in the central nervous system and in the portal vein.

■ COUNTERREGULATION IS IMPAIRED IN TYPE 1 DIABETES

Secretion of the three main counterregulatory hormones normally responsible for rapid reversal of hypoglycemia is severely disrupted in type 1 diabetes.

Night sweats or a clouded mental state on arising should be diligently evaluated

- Insulin secretion is either insignificant or absent.
- Glucagon release during hypoglycemia is also impaired soon after the onset of diabetes, and the plasma glucagon concentration does not increase as it should during hypoglycemia.²² Of interest, however: glucagon is still secreted in response to other glucagon secretagogues, suggesting an acquired signaling defect.²³
- Epinephrine release during hypoglycemia becomes progressively defective in type 1 diabetes; it is not triggered until the plasma glucose level is lower, and the maximal concentration of epinephrine released is significantly reduced.^{24,25} This decrease in epinephrine response during hypoglycemia is accompanied by an attenuated autonomic neural response, which results in the clinical syndrome of impaired awareness of hypoglycemia.²⁶

Without autonomic symptoms, mild hypoglycemia may proceed unnoticed to more advanced and dangerous phases. Patients with impaired awareness of hypoglycemia in addition to defective counterregulation may be at the greatest risk of developing severe hypoglycemia.^{26,27}

Hypoglycemia-associated autonomic failure

Hypoglycemia-associated autonomic failure in type 1 diabetes apparently results from antecedent episodes of mild hypoglycemia that further degrade the counterregulatory response.²⁸

In experiments in people without diabetes, recurrent or recent episodes of hypoglycemia are associated with reduced autonomic (epinephrine and norepinephrine), symptomatic, and cognitive functional responses to subsequent episodes of hypoglycemia, impairing the endogenous defense mechanisms and the clinical signs required for hypoglycemia detection.²⁹ Since patients with type 1 diabetes already have a reduced counterregulatory response (as mentioned above), hypoglycemia-associated autonomic failure may play a role in the vicious circle of hypoglycemia begetting hypoglycemia.

Meticulous avoidance of hypoglycemia in type 1 diabetes can improve the epinephrine response and reverse impaired awareness of hypoglycemia.^{30,31}

HYPOGLYCEMIA IN TYPE 2 DIABETES

Compared with type 1 diabetes, type 2 diabetes poses a much lower risk of hypoglycemia.³² However, given the much larger number of patients with type 2 diabetes and the same clinical rationale for maintaining tight glycemic control, hypoglycemia is a major clinical problem in this population.

Episodes of severe hypoglycemia are much less frequent in patients with intensively treated type 2 diabetes than with type 1 diabetes.^{32,33} However, hypoglycemia becomes progressively more common in patients with type 2 diabetes as they approach the insulin-deficient stage of the disease, when beta cells fail.

Hypoglycemia and oral drugs

Oral antidiabetic medications can be a source of iatrogenic hypoglycemia in patients with type 2 diabetes.

The sulfonylureas account for a substantial proportion of cases of drug-induced hypoglycemia.^{34,35} Because these drugs are widely used, it is difficult to assess the true incidence of hypoglycemia that they cause. Most reported cases of severe hypoglycemia were in patients taking chlorpropamide or glyburide.^{36,37} However, severe episodes characterized by coma have been reported with all the agents in common use.

In part, the hypoglycemic potential of an agent is related to its potency, its plasma and biological half-lives, its metabolism, and the concomitant use of other drugs. For example, liver disease prolongs the hypoglycemic actions of glyburide and glipizide, since these drugs are partially metabolized in the liver. Similarly, kidney disease may prolong the action of insulin (due to impaired clearance) or potentiate the effects of these drugs by other mechanisms.

Sulfonylurea drugs lower plasma glucose by themselves, and they can interact with other agents to cause severe hypoglycemia. The additive (or possibly synergistic) effects during combined insulin and sulfonylurea therapy account for an increasing number of such episodes. Drugs that interfere with sulfonylurea metabolism or compete for circulating plasma protein binding with sulfonylureas can also potentiate these effects.

**On insulin,
the risk of
severe
hypoglycemia
is as high in
type 2 diabetes
as in type 1**



Recently, several new classes of oral agents have been introduced in the United States for the treatment of type 2 diabetes. There is limited experience with most of these agents regarding the risk of hypoglycemia.

Metformin has been available worldwide for 40 years, though its association with hypoglycemia has only recently been quantified. In the United Kingdom Prospective Diabetes Study (UKPDS),³⁸ the frequency of severe hypoglycemia was lower with metformin than with sulfonylureas or insulin, suggesting that when hypoglycemia occurs in patients taking this agent it may be due to other factors or to type 2 diabetes per se, perhaps secondary to hyperinsulinemia.

Nonsulfonylurea insulin secretagogues also can cause hypoglycemia; repaglinide and nateglinide are approved in the United States.³⁹

Thiazolidinediones such as pioglitazone and rosiglitazone sensitize peripheral tissues to insulin and hence may cause hypoglycemia when insulin is used concomitantly, though hypoglycemia can also occur with monotherapy or when these drugs are used in combination with other oral agents, particularly sulfonylureas.⁴⁰

Alpha-glucosidase inhibitors (acarbose and miglitol) are not associated with hypoglycemia, though in theory their use in a patient with hypoglycemia (eg, due to concomitant use of a sulfonylurea) may prevent ingested carbohydrate from being metabolized to glucose in the gut. It is therefore recommended that patients taking alpha-glucosidase inhibitors use oral glucose instead of food to treat episodes of hypoglycemia.

■ CLINICAL APPROACH TO HYPOGLYCEMIA

Patient education

One of the most important things we can do to prevent hypoglycemia is to educate the patient. Education may help to allay the fear of hypoglycemia, an ever-present concern that may substantially impede ideal glycemic control.

Patients with diabetes need to be well informed about:

- The symptoms of hypoglycemia
- The physiologic factors that come into play

- The time course of the drugs they use
- How to prevent and treat episodes of hypoglycemia
- How to monitor their blood glucose levels
- The warning symptoms of hypoglycemia, and to anticipate that typical autonomic symptoms may wane over years of diabetes.

Question the patient carefully

A history of recurrent hypoglycemia should be meticulously investigated, and insulin regimens should be adjusted accordingly.

Carefully question the patient at each visit: probe for details of episodes that the patient recognized as being caused by hypoglycemia, but also assess whether the patient has experienced events that went unrecognized—in particular, neurologic symptoms that required the assistance of a family member but were not identified as severe hypoglycemia. For example, reports of unexplained night sweats or a clouded mental state upon arising in the morning should be diligently evaluated.

It is essential to pay close attention to the history provided by the patient and to the patient's home blood glucose measurements, in part because we lack definitive laboratory measures that can be used to suggest a propensity to severe hypoglycemia.

Patients should be encouraged to document episodes of hypoglycemia and to contact the care team if they have unexpected or more-frequent episodes.

Adjust the insulin regimen

Insulin preparations have different onsets of action, times to peak effect, and effective durations of action—factors that must be considered when adjusting the treatment. This variability affects both glycemic control and hypoglycemic episodes.⁴¹

For example, for preprandial doses, substituting a rapid-acting insulin analogue such as insulin lispro or insulin aspart for regular insulin may reduce the risk of nocturnal hypoglycemia. Similarly, substituting a long-acting insulin analogue such as insulin glargine or insulin detemir for an intermediate-acting insulin such as neutral protamine Hagedorn (NPH) may also reduce the frequency of nocturnal hypoglycemia.^{42,43}

Educating the patient helps allay fear of hypoglycemia, which impedes ideal glycemic control

TABLE 1

Risk factors for severe hypoglycemia in diabetes mellitus

Youth (children)
Elderly taking sulfonylurea drugs
Altered consciousness
Ethanol use
Strenuous exercise in the previous 24 hours
Antecedent hypoglycemia
Use of pentamidine, quinine, or nonselective beta-blocker drugs
Critical illnesses such as sepsis, or hepatic, renal, or cardiac failure
Type 1 diabetes with history of recurrent severe hypoglycemia

5 grams of carbohydrate will increase plasma glucose by about 15 mg/dL

Adjust the oral regimen

Patients on oral antidiabetic drugs are also at risk for developing hypoglycemia. The following factors should be considered:

- Biguanides (metformin), thiazolidinediones (pioglitazone or rosiglitazone) and alpha glucosidase inhibitors (acarbose, miglitol) do not normally cause hypoglycemia. Nonetheless, when combined with insulin or with sulfonylureas, these drugs may potentiate the development of hypoglycemia.
- The insulin secretagogues—sulfonylureas, repaglinide, and nateglinide—are known to induce hypoglycemia in patients with type 2 diabetes. In the case of sulfonylureas, the risk may be greater in the elderly and in patients with altered hepatic or renal function. Among the sulfonylurea drugs, chlorpropamide and glyburide have been reported to be more frequently associated with hypoglycemia.

TABLE 1 lists several risk factors for severe hypoglycemia. Patients in these categories need greater vigilance, both in planning the antidiabetic regimen and in the acute treatment of hypoglycemia.

Acute treatment: Fast-acting carbohydrates

Most mild or moderate episodes of hypoglycemia can be self-treated relatively easily by ingesting fast-acting carbohydrates such as glucose tablets, glucose gels, or food (juices, soft drinks, or a meal).

The suggested amount of carbohydrate to

be ingested is about 15 grams; as a rule of thumb, 5 grams of carbohydrate will increase the plasma glucose concentration by about 15 mg/dL. Importantly, foods that are rich in fat delay glucose absorption, and are thus less effective. If after 15 minutes plasma glucose levels are still below 70 mg/dL and if symptoms have not abated, the patient should take an additional 15 grams of carbohydrate.

Since the glycemic response to oral glucose is relatively transient, ingestion of a snack or a meal shortly after correction of hypoglycemia is recommended.

Parenteral treatment

Parenteral treatment of hypoglycemia is generally recommended if:

- A patient is unwilling or unable to ingest carbohydrates (eg, due to severe hypoglycemia), or
- A patient with type 2 diabetes has sulfonylurea-induced hypoglycemia (which may be prolonged).

Intravenous glucose (25 g) is the preferred treatment for hypoglycemia. Parenteral glucagon (1 mg subcutaneously) is an alternative, especially in patients with type 1 diabetes who may have to be treated by family members for severe hypoglycemia.

Since glucagon stimulates secretion of insulin and also promotes glucose production, it is less effective in patients with type 2 diabetes.

■ NOCTURNAL HYPOGLYCEMIA

A particularly important condition observed mainly in type 1 diabetes is nocturnal hypoglycemia.⁴⁴ It may be asymptomatic and frequently is neither suspected nor identified. Plasma glucose is rarely measured during the night, and nocturnal hypoglycemia may therefore not be confirmed.

Factors that contribute to the development of nocturnal hypoglycemia include increased physical activity in the last 24 hours, imbalance between the antidiabetic regimen and the amount and timing of meals, content of meals (eg, the amount of fat), and alcohol consumption.⁴⁵ In addition, sleep per se is associated with a decrease in the autonomic response to hypoglycemia.⁴⁶



Although most episodes of nocturnal hypoglycemia are asymptomatic, some patients have sleep disturbances (vivid dreams or nightmares), morning headache (feeling hungover), chronic fatigue, or mood changes (mainly depression). Children in particular may present with convulsions or enuresis.⁴⁷

As noted above, recurrent episodes of hypoglycemia cause further deterioration of the counterregulatory response to subsequent hypoglycemia. Thus, nocturnal (and asymptomatic) hypoglycemia may be an important factor in precipitating daily hypoglycemic episodes and exacerbating hypoglycemia-associated autonomic failure.

Strategies to prevent nocturnal hypoglycemia include fine-tuning the insulin regimen, eating “long-acting” bedtime snacks, and regular monitoring of blood glucose at bedtime and before breakfast.⁴⁸ Uncooked starch as a bedtime snack may be particularly effective in preventing nocturnal hypoglycemia due to its slower absorption, but its lack of palatability has limited its widespread use. The bedtime glucose level has been reported to be highly predictive of subsequent hypoglycemia developing during sleep.

Nocturnal glucose monitoring

New, noninvasive glucose monitors are promising.⁴⁹ Not only can such devices provide a continuous profile of blood glucose levels so that treatment can be better adjusted, but some also have audible alarms that can warn the patient of impending hypoglycemia.

A recently approved device for intermit-

tent glucose testing uses iontophoresis to measure interstitial levels of glucose through the skin, without needles (GlucoWatch Biographer; www.glucowatch.com).⁵⁰ The device looks like a large digital watch and has an alarm that can waken the patient if the glucose concentration drops below a predetermined level. However, since the acquisition time required for sample collection using this device is relatively long, and since a lag time may exist between changes in glucose concentrations between the blood and interstitial fluid, the device has limitations as a real-time glucose monitoring device for detection of hypoglycemia.

Further improvements in interstitial fluid glucose monitoring systems are needed, though one such device (the Continuous Glucose Monitoring System or CGMS) is currently approved to provide a retrospective profile of interstitial fluid glucose.⁵¹ Another device currently in late-stage development is a continuous glucose sensor that can report real-time information to the patient.⁵² Ultimately, perfected insulin replacement must be coupled to more precise and frequent determination of glucose concentrations to “close the loop” and avoid the excess insulin that is a factor in causing hypoglycemia.

Other experimental approaches to diabetes treatment (eg, islet cell or pancreatic transplantation), while not applicable to most patients, also carry the promise of reduced likelihood of hypoglycemia, underscoring the central importance of regulated insulin delivery to the maintenance of glucose homeostasis.⁵³ ■

**Nocturnal
hypoglycemia
is often
undetected**

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