

Educating Patients About Hypoglycemia Prevention and Self-Management

Jeff Unger, MD

Case Presentation

Mrs. B was a 68-year-old, Asian-American woman with a 15-year history of type 2 diabetes. Her coexisting medical conditions included unilateral intraductal carcinoma of the breast, which was treated with a modified radical mastectomy 6 years ago and showed no evidence of recurrence. Although there was no history of alcohol use, her liver function studies had been elevated to two times the upper limit of normal for several years. A liver biopsy revealed the presence of nonalcoholic steatohepatitis (NASH). She was admitted to the hospital on one occasion within the past year for bleeding esophageal varices.

Mrs. B had no history of macrovascular disease, chronic kidney disease, retinopathy, or neuropathy. For the past 10 years, she had taken 10 mg glyburide daily. Her primary care provider (PCP) was concerned that her A1C had increased from 7.4 to 7.9% in the past 6 months.

Her family members stated that they rarely spoke about diabetes, self-monitoring of blood glucose (SMBG), or diabetes-related complications. In fact, the patient's 72-year-old husband also has type 2 diabetes and is undergoing dialysis. In the past year, Mr. B has had at least two episodes of severe hypoglycemia that required hospitalization. He blames his end-stage renal disease on medication he is taking to control his blood glucose levels.

Because of concerns about Mrs. B's increasing A1C, her PCP asked her to consult with a local endocrinol-

ogist who added basal insulin to her diabetes treatment regimen. She was not provided with any specific instructions about how to inject the basal insulin or when to perform SMBG. Her son noted that she tended to get "confused," but he did not attribute this to her blood glucose level because he never saw her checking her glucose. Her handwritten glucose log showed several readings in the low 50 to 60 mg/dl range, but a pattern of hypoglycemia could not be determined.

One month after beginning the combination therapy of glyburide and basal insulin, Mrs. B was observed to be driving 90 mph in the wrong direction on a residential street. After swerving to miss several cars, she lost control of her vehicle, hit a tree, and was killed on impact.

Spontaneous hypoglycemia is uncommon in the nondiabetic population but constitutes the primary barrier to optimal glycemic control in people with diabetes.

The pathogenesis of type 1 diabetes can be viewed as a bihormonal defect. Patients experience an absolute deficiency of insulin production and secretion as a result of autoimmune destruction of pancreatic β -cells coupled with exaggerated excretion of glucagon production by pancreatic α -cells. Over time, the loss of glucose counterregulation results in a higher likelihood of developing hypoglycemia that cannot be reversed by endogenous hormonal interventions.

Patients with type 2 diabetes can experience hypoglycemia resulting from medications that trigger insulin release in a glucose-independent manner. Over time, counterregulatory communication between the glucagon-producing α -cells and the insulin-producing β -cells becomes physiologically dysfunctional, thereby increasing the risk of hypoglycemia.

Patients with coexisting disorders such as cirrhosis, eating disorders, chronic kidney disease, cardiovascular disease, and advanced age are at high risk for mortality because of acute, severe hypoglycemic events.

Physicians and ancillary practitioners have the responsibility to teach patients with diabetes how to predict, avert, and correctly manage hypoglycemia. Patients with hypoglycemia awareness adrenergic failure (HAAF) should be encouraged to use continuous glucose monitoring (CGM) devices, which can proactively alert them to impending hypoglycemic events.

Definition of Hypoglycemia

A hypoglycemia and diabetes work group of the American Diabetes Association and The Endocrine Society has recommended that a plasma concentration ≤ 70 mg/dl should be the cut-off value for defining the upper boundary of hypoglycemia.¹ Although this value is higher than the threshold of hypoglycemia symptoms, patients can prepare to take corrective action

Table 1. Subclassification of Hypoglycemia¹

Classification of Hypoglycemia	Plasma Concentration	Description
Severe hypoglycemia	May not be known to patient, but neurological recovery after the glucose correction is considered evidence that the event was induced by hypoglycemia	Requires the assistance of another person to actively administer carbohydrate or glucagon or to take other corrective actions
Documented symptomatic hypoglycemia	≤ 70 mg/dl	Typical symptoms of hypoglycemia are accompanied by a documented plasma glucose level ≤ 70 mg/dl
Asymptomatic hypoglycemia	≤ 70 mg/dl	No symptoms noted, but blood glucose is noted to be ≤ 70 mg/dl
Probable symptomatic hypoglycemia	—	Symptoms typical of hypoglycemia are not accompanied by a plasma glucose determination but are presumed to be associated with a plasma level ≤ 70 mg/dl
Pseudo-hypoglycemia	≥ 70 mg/dl	Patient reports symptoms typical of hypoglycemia, yet the blood glucose levels are ≥ 70 mg/dl

when their blood glucose levels drop to < 70 mg/dl before developing defective hormonal counterregulation. The subclassifications of hypoglycemia are shown in Table 1.

Prevalence of Hypoglycemia

Patients with type 1 diabetes may experience plasma glucose concentrations < 50 mg/dl as often as 10% of the time. Defective glucose counterregulation may occur within 1 year of being diagnosed with type 1 diabetes. Typical patients with type 1 diabetes will experience two episodes of symptomatic hypoglycemia weekly and thousands of events during their lifetime.^{2,3}

The frequency and severity of hypoglycemia in patients with type 2 diabetes is often underestimated by clinicians. Unfortunately, patients fear the adrenergic symptoms associated with treatment-emergent hypoglycemia. Once they become a “victim” of hypoglycemia, they may be reluctant, or even resistant, toward intensified regimens designed to achieve recommended glycemic goals.⁴

The risk of hypoglycemia in patients with insulin-requiring type 2 diabetes is equal to that in patients with type 1 diabetes. The Diabetes Audit and Research in Tayside, Scotland study⁵ determined that the prevalence of hypoglycemia among people with type 1 diabetes was 7.1%, compared to 7.3% in its cohort of people with insulin-treated type 2 diabetes. Thus, patients with type 2 diabetes of long duration who require insulin are at higher risk of developing hypoglycemia than are treatment-naïve individuals starting insulin for the first time.⁴

The incidence of hypoglycemia is particularly high among patients treated with insulin over extended periods of time, again reinforcing the idea that advanced disease progression and increased insulin use subsequently escalate the risk of hypoglycemia. The U.K. Hypoglycemia Study Group found that the incidence of severe hypoglycemia in patients with type 1 diabetes treated with insulin for > 15 years was three times higher than in those treated with insulin for < 5 years. The prevalence of

hypoglycemia in patients with type 2 diabetes exposed to insulin therapy for > 5 years is 25%, a threefold increased risk compared to individuals exposed to insulin for < 2 years.² Clinicians and educators should reinforce the importance of hypoglycemia prevention, detection, and reversal for all patients with type 1 diabetes and for those with type 2 diabetes who have used insulin for > 5 years.

Consequences of Hypoglycemia

Effect of hypoglycemia on morbidity and mortality rates

Hypoglycemia increases the risk of cardiovascular and all-cause mortality in patients with diabetes.⁶ Severe hypoglycemia is associated with a macrovascular events hazards ratio (HR) of 2.88 and a microvascular events HR of 1.81. The mortality HR for a hypoglycemic event in patients with type 2 diabetes is 2.69.⁶

Hypoglycemia during hospital admissions is associated with increased lengths of stay and with increased 1-year mortality and inpatient mortality rates (2.96%

for patients who had at least one hypoglycemic episode during the hospitalization vs. 0.82% for patients who had none).⁷

Neurological impairment after a hypoglycemic event

Because the brain depends on glucose as an obligate energy source, a reduction in available glucose reserves can result in serious neurological consequences. Both mood and memory are impaired after a single episode of hypoglycemia.⁸

Plasma blood glucose levels of < 40 mg/dl will result in neuroglycopenia, which is associated with altered levels of consciousness, coma, and death. Severe neurological sequelae are relatively rare, even in patients who experience frequent hypoglycemia. Glucose levels < 50 mg/dl can interfere with patients' ability to perform everyday tasks, resulting in cognitive deterioration, irritability, belligerent behavior, fatigue, visual failure, dysarthria, disorientation, coma, and seizures.⁹ Hypoglycemia-induced dementia has been observed in elderly patients, although the mechanism by which cognitive impairment occurs is not clear.¹⁰

Recurrent hypoglycemia lowers or even eliminates the blood glucose concentration threshold at which patients develop a sympathetic response likely to prompt them to take evasive action in time to reverse an impending event. Elderly patients may lose their balance without warning, falling to the ground. The subsequent confusion after such a fall is likely to be attributed to "the aging process" rather than to deficient glucose counterregulation.

Prolongation of a hypoglycemic event is likely to result in subsequent episodes within a 24-hour period. Aberrant behavior and structural damage to the brain may occur with repeated episodes of hypoglycemia.

**Hypoglycemia awareness
autonomic failure**

Repeated hypoglycemic events can lead to HAAF, a neurological condition affecting one's ability to perceive the autonomic features of low blood glucose levels. Patients with HAAF become defenseless and

unable to reverse an impending event. Adults with type 1 diabetes who have impaired awareness of hypoglycemia are much more likely to be exposed to asymptomatic hypoglycemia and are at higher risk of developing severe hypoglycemia than those who are able to detect a drop in plasma glucose.



Figure 1. This CGM tracing of a 28-year-old patient with a 15-year history of type 1 diabetes demonstrates the occurrence of hypoglycemia unawareness lasting from 9:00 to 10:30 p.m. The patient experiences a 2-hour episode of hypoglycemia unawareness while sleeping from 11:30 p.m. until 2:00 a.m., when he is finally awakened by his CGM alarm and successfully corrects his hypoglycemia. Reprinted with permission from Unger J: Diabetes Management in Primary Care. 2nd ed. Philadelphia, Pa., Lippincott, Williams, and Wilkins, 2012.

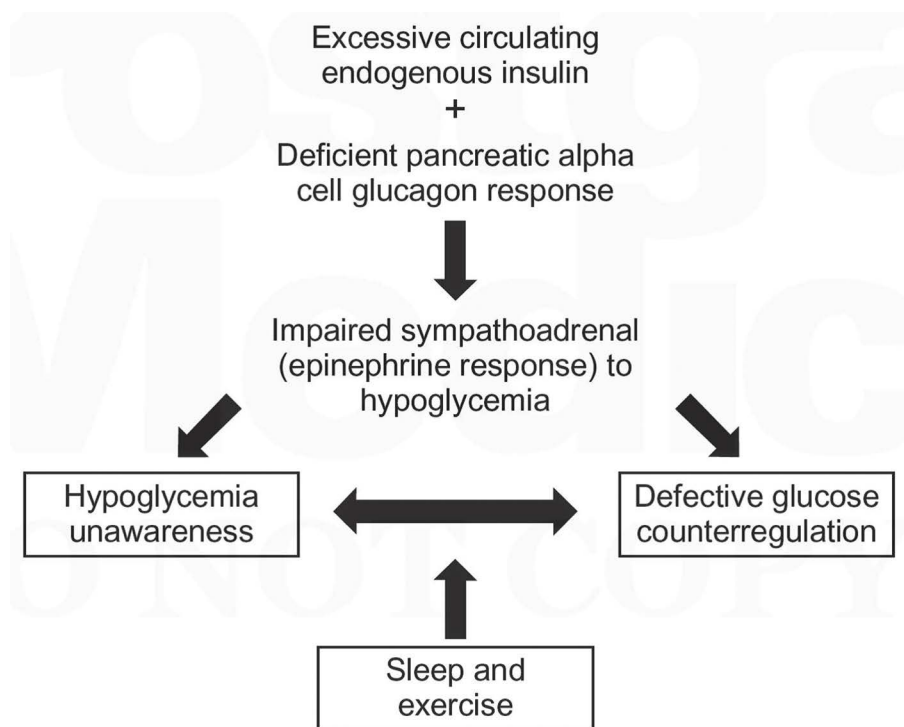


Figure 2. Mechanisms associated with HAAF. Reprinted with permission from Ref. 9.

Patients with type 1 diabetes and HAAF have double the frequency of hypoglycemic events (7.9 vs. 3.7 events in those with normal awareness), seven times the incidence of asymptomatic hypoglycemia (3.7 vs. 0.5 events), and an annual prevalence of severe hypoglycemia of 53 versus just 5% in those with normal awareness.¹¹ Figures 1 and 2 depict the mechanisms associated with HAAF.

Euglycemic individuals signal glucagon secretion via a reduction in insulin release by pancreatic β -cells, coupled with low glucose stimulation of α -cells. In people with type 1 diabetes, a signaling defect between the α - and β -cells accounts for failure to mount an acceptable counterregulatory response during hypoglycemia. With the autoimmune destruction of glucose-dependent β -cell insulin secretion, signaling pathways between the α - and β -cells become disrupted. Loss of the glucagon secretory response to hypoglycemia is a key feature of HAAF. An attenuated epinephrine response to hypoglycemia completes the syndrome of defective counterregulation. Without glucagon secretion or epinephrine counterregulation, patients are 25 times more likely to experience a severe hypoglycemic event with intensive insulin therapy.¹²

A single hypoglycemic event in patients with type 1 diabetes results in defective counterregulation and delayed reversal of hypoglycemia. Epinephrine secretion and mobilization in response to a subsequent reoccurrence of hypoglycemia in a clinical setting, during which circulating endogenous insulin levels remain elevated and pancreatic α -cell glucagon production is absent, is the hallmark of HAAF. Because both defective glucose counterregulation and HAAF contribute to an increased frequency of hypoglycemia, the incidence of hypoglycemic

induction extends into periods when patients sleep, as well as exercise.¹³

Economic impact of hypoglycemia

A number of health economic studies have evaluated the negative impact of hypoglycemia on society in both the United States and Europe. One study,⁵ conducted in the United Kingdom, examined 244 episodes of severe hypoglycemia in 160 patients with diabetes in 1 year. Each episode of hypoglycemia cost ~\$600. The direct and indirect costs of a single severe hypoglycemic event in the United States have been estimated at \$1,500, including emergency department evaluation and lost work productivity.¹⁴

Nocturnal hypoglycemia results in patients arriving late to work or missing entire days at the office. Patients who experience hypoglycemia are likely to use extra test strips for fear of having a recurrence of low blood glucose levels. Calls to doctors for guidance on glucose management are increased after an episode of hypoglycemia, and patients often inappropriately self-titrate their medications to avoid future events.¹⁴

Clinical characteristics of hypoglycemia in the elderly

Hypoglycemia may have severe consequences in the elderly but is often overlooked by both patients and clinicians. The estimated occurrence of hypoglycemia in patients > 65 years of age is ~1.4 episodes/100 patient-years.¹⁵ The risk of hypoglycemia is augmented in elderly patients taking insulin, those with cirrhosis, and those with HAAF or renal insufficiency. Acute and potentially life-threatening consequences of hypoglycemia in elderly patients include acute myocardial infarction, ventricular rhythm disorders, stroke, and injuries from falls.¹⁶

High-risk hours for hypoglycemia in the elderly population are

toward dinnertime (for patients taking sulfonylureas) or at the end of the morning and afternoon in those taking rapid-acting insulin.¹⁶ Polypharmacy, advanced age, and a recent hospitalization favor hypoglycemia in this high-risk population.¹⁷

Age-related impairment in counterregulatory hormone responses has been described in elderly patients with respect to glucagon and growth hormone secretion.¹⁸ Declines in renal function and hepatic enzyme activity may also interfere with the metabolism of sulfonylureas and insulin, thereby potentiating their hypoglycemic effects. Hypoglycemia may be prolonged in patients using sulfonylureas, especially those who have chronic renal insufficiency.¹⁹

Impact of hypoglycemia on pregnancy

Normal plasma glucose levels are ~20% lower during pregnancy. Fasting glucose levels average 75 mg/dl, whereas postprandial elevations peak at 110 mg/dl.²⁰

Attempts to attain strict glycemic control during pregnancy may be compromised by the risk of inducing severe hypoglycemia, which occurs in 45% of patients with type 1 diabetes. When pregnant women and nonpregnant women are compared using CGM, mild hypoglycemia (defined as blood glucose < 60 mg/dl) is more common in pregnancy.²¹

Women with type 1 diabetes experience three times more hypoglycemia during the first trimester of pregnancy than when they are not pregnant. Hypoglycemia rates tend to decline during the third trimester.²² Using CGM may help to reduce the number of severe hypoglycemic events in pregnancy.^{23,24}

Maternal hypoglycemia generally does not increase risks to the fetus as long as pregnant women avoid injury during hypoglycemic episodes.²⁵ Table 2 lists the risk factors for hypoglycemia during pregnancy.

Table 2. Risk Factors for Hypoglycemia During Pregnancy and Postpartum¹

- History of severe hypoglycemia within the preceding year
- History of HAAF
- Low A1C during first trimester
- Glycemic variability
- Insulin stacking when correcting postprandial hyperglycemia
- Breastfeeding

Risks of driving while experiencing hypoglycemia

A meta-analysis of 15 studies²⁶ suggested that the relative risk (RR) of having a motor vehicle accident for people with diabetes compared to the general population ranges between 1.126 and 1.19%. When compared to patients with other medical conditions such as attention deficit/hyperactivity disorder (RR 4.0) and obstructive sleep apnea (RR 2.4), patients with diabetes are no more likely to be involved in an accident than their euglycemic counterparts.^{27,28}

Still, the risk of hypoglycemia-induced motor vehicle accidents is of concern to patients and to government driving regulatory agencies. Driving risk assessment is often overlooked by busy clinicians. Only 62% of health care providers recommend that patients test their blood glucose levels before driving, and 13% of clinicians believe that people can safely operate a motor vehicle when their blood glucose level is < 72 mg/dL.²⁹ Nearly half of all drivers with type 1 diabetes and 75% of those with type 2 diabetes have never discussed driving guidelines with their physician.³⁰

Patients at highest risk for collisions are those with a recent history of hypoglycemia, regardless of the prescribed treatment regimen.³¹ Drivers with a history of hypoglycemia-related accidents are at higher risk for having another collision

compared to individuals who have been accident free. A hyperinsulinemic clamp study³² was performed on type 1 diabetes patients with and without a history of hypoglycemia-related accidents who were placed in a driving simulator. As hypoglycemia developed, those who had had previous accidents were observed to drive more recklessly and were noted to release less epinephrine in response to the hypoglycemic induction. This defect in counterregulation would allow patients to slip into a deeper and more prolonged phase of hypoglycemia.³²

Patients with a history of motor vehicle accidents have been noted to have impaired glucose counterregulation, are more insulin sensitive, and experience difficulty with working memory and speed processing in both euglycemic and hypoglycemic states.³³ Thus, any patients with type 1 diabetes who have been in a recent car accident should be carefully evaluated for HAAF and educated about the effects of driving while hypoglycemic.³¹

Acute insulin-induced hypoglycemia causes significant impairment in spatial cognitive abilities and mental processing.³⁴ While driving, patients may be able to maintain their grip on the steering wheel, yet become disoriented as to their driving location and direction of navigation. Driving the wrong way on a residential street would be an example of spatial impairment. Table 3 may be used to identify drivers who are potentially at risk and who may require further evaluation and intensive hypoglycemia prevention protocols to minimize their likelihood of motor vehicle accidents.³⁵

Having a history of hypoglycemia does not implicate patients as being unsafe drivers. However, patients with a history of severe hypoglycemia should be evaluated to determine the cause, whether it was isolated or recurrent, and how best to mitigate future risks. Recurrent episodes of severe hypoglycemia (defined as two or more events within a 12-month period) may warrant reporting to the appropriate licensing agency indicating that such

Table 3. Drivers Who May Be at Risk for Motor Vehicle Accidents Because of Hypoglycemia

Individuals at risk for motor vehicle accidents include those:

- Who have experienced an episode of severe hypoglycemia within the past 24 months
- Who have had to have others drive on their behalf because of the presence of hypoglycemia
- Who have had a collision in the past 12 months, especially when the accident was attributed to hypoglycemia
- With HAAF
- With coexisting diabetes and obstructive sleep apnea
- Using a sulfonylurea in combination with insulin and benzodiazepines
- Who use insulin and abuse alcohol or drink while skipping meals; alcohol exacerbates the cognitive impairment associated with hypoglycemia³⁵
- Using a sulfonylurea and insulin who have chronic kidney disease
- With sensory neuropathy
- With erratic sleep and meal schedules
- On insulin therapies who are nonadherent to SMBG
- Who have limited understanding of how to monitor for and reverse hypoglycemia

patients should not drive until their deficiencies in diabetes self-management are addressed.³¹

High-risk patients should monitor their blood glucose levels before driving and at 1-hour intervals while on long trips. Considerations should be given to factors that may predict a decrease in blood glucose levels, such as insulin dose timing, timing of the last meal, and exercise type and timing. All cars driven by such patients should be equipped with a spare glucose testing meter, as well as a quick source of carbohydrate, which can be stored even in a hot vehicle. Glucose tabs, liquid glucose “shots,” and glucose gel may all be placed in the glove compartment and consumed in an emergency. Each 15 g of carbohydrate will raise plasma glucose ~ 75 mg/dl within 15 minutes.

At the first sign of hypoglycemia, individuals should safely exit the road and consume the carbohydrate. Driving should not resume until their blood glucose is safely on the rise > 70 mg/dl and their cognition has recovered.

Reducing the Risk of Hypoglycemia

Patient education

Patient education has been shown to improve outcomes from hypoglycemia, but not to reduce the incidence of events.³⁶ Medications that are likely to result in hypoglycemia should be reviewed with patients and their family members on a regular basis. Hypoglycemia symptom recognition and management should be discussed at each visit. Written instructions should also be provided to all patients, because caregivers might panic and not remember directions for reversing hypoglycemia in an emergency situation. Patients should be advised to notify their clinicians if they are experiencing hypoglycemic events so that appropriate

adjustments may be made in their treatment regimens.

Some patients with an elevated A1C may experience acute adrenergic symptoms, including lightheadedness, sweating, weakness, fatigue, and palpitations, although their plasma glucose levels remain well above 70 mg/dl. These symptoms are uncomfortable but self-limiting. Dose modifications may be needed as patients adjust to their prescribed therapeutic regimens.

Dietary interventions

Carbohydrates raise blood glucose levels. Patients must understand which carbohydrate choices might be the most appropriate to rapidly

reverse hypoglycemia. Table 4 provides a detailed treatment plan for managing hypoglycemia.^{37,38} Patients who are using mixed insulin analogues should also avoid skipping meals because this may trigger hypoglycemia.

Dissociated meal and insulin injection patterns lead to glycaemic variability and hypoglycemia. Assuming a premeal glucose level > 80 mg/dl, insulin should be injected 15 minutes before eating so that the rise in insulin concentration will match the time to peak carbohydrate absorption from the gut once the meal is eaten. If the glucose level is < 80 mg/dl, the injection should be given either at mealtime or immediately after eating.³⁹

Table 4. A Strategic Approach to Reverse Hypoglycemia^{37,38}

- If blood glucose is ≤ 60 mg/dl:
 - Eat or drink 15 g of carbohydrate
 - Recheck blood glucose after 15 minutes. If the reading is ≤ 60 mg/dl, repeat treatment with an additional 15 g of carbohydrate
 - Retest blood glucose after 15 minutes
 - If blood glucose remains ≤ 60 mg/dl, repeat treatment with an additional 15 g of carbohydrate and contact your health care provider
- A useful formula to help patients emerge safely from hypoglycemia without causing rebound hyperglycemia:
 - $(100 - \text{blood glucose}) \times 0.2 = \text{g of carbohydrate needed for appropriate blood glucose correction}$
 - Thus, if blood glucose is 50 mg/dl, consume $100 - 50 = 50$; $50 \times 0.2 = 10$ g of carbohydrate
- Examples of foods containing 15 g of carbohydrate:
 - Glucose tablets (3- to 5-g tablets)
 - 4 oz of juice or regular soda
 - 1 Tbsp of honey or table sugar
 - 1 small box of raisins
 - 1 bottle of glucose “shot” liquid
- Patients with a history of HAAF should have access to a glucagon emergency kit at home and in their work place. Patients with severe hypoglycemia who cannot be aroused should be injected with glucagon, 1 mg intramuscularly, by a family member or associate. This should result in a rapid reversal of hypoglycemia.
- Patients who become hypoglycemic while using α -glucosidase inhibitors (AGIs; acarbose or miglitol) will not respond to sucrose. Oral glucose (dextrose) should be used to treat hypoglycemia because its absorption is not inhibited by AGIs. Glucagon will also effectively reverse hypoglycemia.

Preventing hypoglycemia while exercising

Exercise increases glucose utilization by skeletal muscles and increases the risk of hypoglycemia. The risk factors for exercise-induced hypoglycemia include prolonged physical activity, unaccustomed exercise intensity and mode (e.g., a patient who runs on a treadmill daily but now decides to go cross-country skiing), inadequate carbohydrate intake in relation to ambient insulin “on board” (insulin from a previous dose that is still active), HAAF, and failure to perform SMBG before and during exercise.

The risk of exercise-induced hypoglycemia may be mitigated by performing SMBG before and within 30 minutes of ending exercise sessions. The pre-exercise glucose target should be 120–180 mg/dl. Lower blood glucose levels should be treated before exercise by consuming 15 g of carbohydrate.⁴⁰

Adjusting insulin doses before exercise is prudent. If exercise will be occurring within 4 hours of using prandial insulin, the dose should be reduced by 50%. Programmable insulin pumps allow patients to set a temporary basal rate of insulin delivery while exercising or to stop insulin flow before initiating exercise. Patients who exercise on a regular schedule may also program a lower basal rate to coincide with anticipated exercise sessions each day.³⁹

Medication adjustment

Medications should be reviewed at each office visit. If patients appear to be experiencing hypoglycemia, pattern (structured) glucose testing may prove beneficial in determining which therapeutic alterations require active changes.⁴¹ Initially, medications that result in fasting hypoglycemia should be adjusted. The second area of concern would be diurnal hypoglycemia, followed by postprandial hyperglycemia (Figure 3).

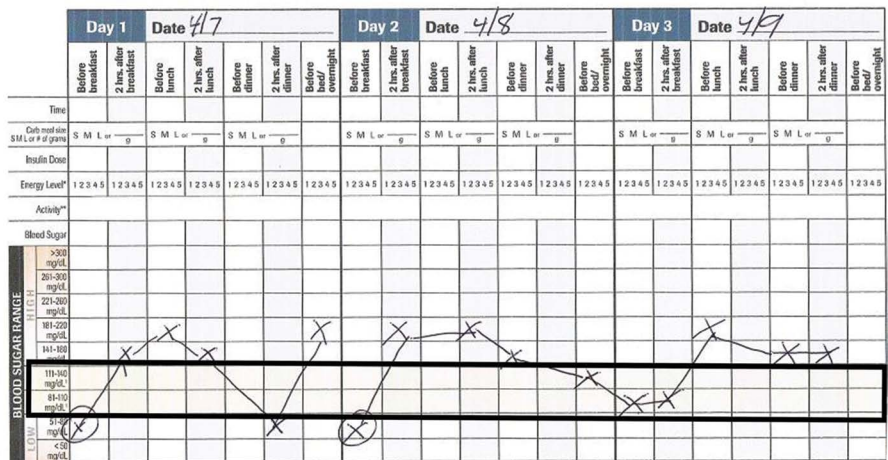


Figure 3. Glucose log of a 51-year-old patient with insulin-requiring type 2 diabetes and an A1C of 7.8% who takes 10 mg of glyburide at bedtime and 25 units of basal insulin at 9:00 p.m. The patient is asymptomatic but noted that she was awakening on two or three mornings with blood glucose values < 70 mg/dl. Her glyburide was discontinued and replaced with a dipeptidyl peptidase-4 inhibitor.

Medication adjustments should be made for patients who have chronic kidney disease (CKD). Most glucose-lowering agents (including metformin, glimepiride, pioglitazone, exenatide, sitagliptin, saxagliptin, pramlintide, insulin, and glinides) undergo some renal clearance. As a consequence, clearance may be delayed, resulting in higher plasma blood levels of these drugs. Patients with advanced CKD (stages 3–5) should have their medications reviewed and doses adjusted when their creatinine clearance is < 50 ml/min/1.73 m². The exceptions to this rule are liraglutide and linagliptin, which require no dosing adjustments.⁴²

Chronic kidney disease increases patients’ risk for both acute hypoglycemia and HAAF. Insulin suppresses glucagon secretion, which, in turn, leads to impaired gluconeogenesis and hypoglycemia counterregulation. Clinicians should consider reducing the total daily dose of insulin by 25% in hospitalized patients with a glomerular filtration rate < 45 ml/min/1.73 m² to minimize the risk of hypoglycemia.⁴³

Glucose monitoring

Although glucose monitoring is essential in managing diabetes, structured (patterned) glucose testing provides an effective means by which patients may predict impending hypoglycemia.⁹ Structured glucose testing allows patients and physicians to identify specific glycemic patterns that may be corrected with pharmacological or lifestyle interventions. The patterns easiest to identify and most often amenable to therapeutic intensification include hypoglycemia, fasting hyperglycemia, and postprandial hyperglycemia. Testing should be performed before and 2 hours after each meal for 3 days before patients’ next scheduled appointment.

The difference between the baseline premeal and 2-hour postprandial blood glucose levels is referred to as the Δ (or “delta,” a math symbol indicating the difference between two values). A “physiological” response to a meal should result in a positive Δ of 0–50 mg/dl. For example, a patient checks his blood glucose before eating dinner and notes the level as 125 mg/dl. He then determines that

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9 units of insulin will be required for that meal. He injects the insulin 15 minutes before eating because his premeal glucose is > 80 mg/dl. His 2-hour postprandial glucose level is 145 ($\Delta = +20$ mg/dl). Thus, the patient gave the correct amount of insulin to cover the amount of carbohydrate consumed in that meal.

The presence of any negative Δ value 2 hours postprandially is worrisome and implies that a mismatch occurred between the insulin bolus dose and the amount of carbohydrate consumed. If the patient's 2-hour postmeal glucose had been 100 mg/dl, his Δ would have been -25 mg/dl. Because rapid-acting insulin has a duration of action of 4 hours, the patient would have known that his blood glucose level is actually decreasing. Performing SMBG again in 1 hour would appear to be a prudent response to the negative Δ value. The patient could then take a corrective action if he continued to show evidence of a decrease in his glucose value.

Using CGM devices

Although SMBG regimens such as before and after meals and periodically in the middle of the night can help predict and may minimize the risk of developing hypoglycemia, CGM technology allows patients to receive real-time notification of impending events, either through preset alarms or simply by looking at the device display.⁹ The devices consist of three components: a disposable sensor that measures the current or signal generated by the presence of glucose, a transmitter that is attached to the sensor and powers the electrical chemical glucose reaction in the device, and a receiver that displays and stores glucose information. Using an applicator or insertion device, patients insert a sensor wire under their skin. The transmitter sends a radiofrequency signal to the receiver,

where it is translated into a glucose value. The sensor values are paired to capillary blood glucose values through periodic calibration using capillary blood glucose obtained from a fingerstick to ensure ongoing accuracy of the sensor throughout its wear time (3, 5, or 7 days, depending on the CGM system). CGM devices not only display real-time interstitial glucose values, but also sound auditory alerts for extreme changes in glucose values.

Patients with type 1 diabetes have evidence of dysfunctional glucose counterregulation during sleep and are therefore at greater risk of developing nocturnal hypoglycemia and HAAF.⁴⁴ Endogenous concentrations of epinephrine and norepinephrine are reduced during sleep. Other aspects of sympathetic activity, including pulse, blood pressure, and vascular resistance, are mitigated during non-REM sleep in patients with diabetes. Thus, patients who experience nocturnal hypoglycemia are unlikely to reverse the events through normal counterregulatory pathways. Nocturnal hypoglycemia will likely carry over to impair counterregulation during the next day. Patients with a history of HAAF or nocturnal hypoglycemia should be placed on CGM.⁹

Case Discussion: Mrs. B and Hypoglycemia

Let us now analyze the case of Mrs. B, described at the beginning of this article, as it relates to hypoglycemia. This patient had a 15-year history of type 2 diabetes; a long duration of disease increases the likelihood of developing hypoglycemia as a result of defective counterregulation. Mrs. B also has a history of NASH, which decreases insulin clearance and appears to increase the sensitivity of pancreatic β -cells to produce endogenous insulin when exposed to sulfonylureas.⁴⁵ In addition, she had a

history of breast cancer and multiple comorbidities.

Mrs. B was referred to an endocrinologist by her PCP for possible intensification of treatment with insulin to address her deteriorating glycemic control. Her family members noted that she had periods of confusion while taking metformin and glyburide, but she did not perform SMBG regularly. A review of her written logs of SMBG within the past 30 days did reveal two worrisome values (55 and 52 mg/dl).

One might argue that a safe A1C target for Mrs. B would have been in the range of 7.5–8%. Nevertheless, her endocrinologist prescribed basal insulin, continued her sulfonylurea, and discontinued her metformin. Mrs. B and her family were not provided with SMBG instructions or education regarding identifying and reversing hypoglycemia.

One month after starting her basal insulin + glyburide regimen, Mrs. B awoke with a blood glucose of 82 mg/dl. Family members do not recall if she ate breakfast that morning. Six hours later, she died in an accident after driving on the wrong side of a street at a high speed.

Sulfonylureas will result in hypoglycemia in the middle of the afternoon, ~ 6 –8 hours after they are consumed. Mrs. B's loss of spatial recognition and disorientation secondary to hypoglycemia resulted in her demise.

Future Perspectives

A closed-loop insulin pump-CGM system (also known as a sensor-augmented insulin pump) is being investigated as a means by which intensively managed patients with type 1 diabetes may minimize their risk of treatment-emergent hypoglycemia. Under experimental conditions, closed-loop devices have demonstrated superiority over the current open-loop system in allowing

patients to achieve a greater amount of time within a designated glycemic target range while experiencing less hypoglycemia.⁴⁶ Sensor-augmented pumps, which are now available in Europe and are under Food and Drug Administration review in the United States, automatically discontinue basal insulin delivery when a pre-set interstitial hypoglycemic threshold is breached.

Conclusions

Iatrogenic hypoglycemia is a substantial barrier to the effective control of blood glucose concentrations in patients with type 1 or type 2 diabetes. Hypoglycemia can have a significant impact on morbidity and mortality, increase the length of hospital stays and health care costs, and negatively affect a person's ability to safely operate a motor vehicle. Patients with diabetes should be educated on ways they can reduce their frequency of hypoglycemic events and reduce their likelihood of developing defective glucose counterregulation.

Physicians should assess medications and SMBG logs at each visit. Appropriate and timely adjustments in medication may reduce patients' risk of experiencing hypoglycemia and HAAF. Structured glucose testing is preferred over random sampling. CGM is recommended for patients who experience HAAF.

Elderly patients should be carefully evaluated for coexisting medical problems such as CKD, liver failure, and coronary artery disease. Hypoglycemia symptoms in elderly patients are often inappropriately attributed to the aging process rather than to actual decline in plasma glucose levels.

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Jeff Unger, MD, is director of the Catalina Research Institute in Chino, Calif.