

# Strategies to Limit the Effect of Hypoglycemia on Diabetes Control: Identifying and Reducing the Risks

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Individuals with diabetes, their families, and health care providers (HCPs) often cite hypoglycemia as the limiting factor to achieving optimal diabetes control. Hypoglycemia is a reality for people with type 1 diabetes and for many with type 2 diabetes.

According to Cryer,<sup>1</sup> the average person with type 1 diabetes suffers two episodes of hypoglycemia per week and one episode of severe hypoglycemia per year. Severe hypoglycemia is less common in those with type 2 diabetes. However, in the U.K. Prospective Diabetes Study (UKPDS), 0.7% per year of patients taking a sulfonylurea and 2.3% per year of those using insulin experienced severe hypoglycemia. Among patients with type 2 diabetes, the greatest frequency of hypoglycemia is found in those on insulin.<sup>2</sup>

The body's normal response to hypoglycemia is significantly altered in diabetes, as well as by the use of exogenous insulin or insulin secretagogues. Thus, the physiological symptoms and negative consequences of hypoglycemia may result in significant fear of hypoglycemia and anxiety associated with possible hypoglycemia for individuals with diabetes.<sup>3</sup> In addition, HCPs may not intensify therapy for fear of inducing hypoglycemia.<sup>4</sup> Hypoglycemia has been noted as the limiting factor for many patients in achieving euglycemia.

Yet, pivotal studies such as the UKPDS and the Diabetes Control

and Complications Trial leave no doubt that improved glycemic control prevents or delays microvascular complications and may also reduce macrovascular events.<sup>2,5</sup> Therefore, HCPs and patients alike must seek to achieve euglycemia while limiting hypoglycemia. The risk of hypoglycemia should not be used as an excuse for less-than-optimal glucose control.

## Defining Hypoglycemia

A glucose level of < 70 mg/dl is generally accepted as the glucose alert level at which individuals with diabetes should take action. The American Diabetes Association (ADA) Workgroup on Hypoglycemia did not define hypoglycemia as it traditionally has been presented in most educational materials (i.e., mild, moderate, or severe).<sup>6</sup> Instead, it classified hypoglycemia as symptomatic, asymptomatic, and severe.

The guiding principal behind this decision was that, to prevent hypoglycemia, individuals with diabetes should assess and likely take some preventive action earlier; thus, the term "symptomatic" was adopted. "Severe" hypoglycemia is defined as any event requiring assistance from another person. This would include any level of unconsciousness. These levels were also established to aid in improving consistency of reporting for research studies.

Patients who lose their ability to sense impending hypoglycemia,

referred to by the Working Group as "asymptomatic," are known to have hypoglycemia unawareness. This unawareness occurs as impairment in epinephrine release and other normal physiological responses to hypoglycemia and limits individuals' ability to respond appropriately to impending low blood glucose. The usual warning symptoms such as shakiness, sweating, and irritability are absent.

Without these adrenergic responses, such individuals only develop neurological symptoms such as confusion, at which time they are unable to take action to treat their low blood glucose and therefore develop severe hypoglycemia.

Hypoglycemia unawareness was once associated with longstanding diabetes but is now known to occur as a result of increasing frequency of hypoglycemia and not just longer duration of the disease. Avoidance of hypoglycemia for several weeks may lead to improved hypoglycemia awareness.<sup>7</sup> A vicious circle of hypoglycemia can occur if hypoglycemia awareness is not restored.<sup>8</sup>

With careful evaluation of medication recommendations, use of physiological insulin replacement strategies, provision of self-management education, psychological support for individuals and families, and a "checklist" type of investigative strategy, the limiting factor of hypoglycemia can be minimized while achieving optimal diabetes control. Hypoglycemia should not

be viewed as an insurmountable barrier, but rather as an opportunity to potentially improve a recommended medication strategy, improve on daily diabetes care practices, or uncover other medical diagnoses that may be contributing to the development of hypoglycemia.

**Investigating the Causes and Effects of Hypoglycemia**

How can HCPs assist individuals with diabetes in identifying potential risk factors for the development of hypoglycemia or identifying the causes of hypoglycemia events? The cause may seem obvious: either the diabetes medication, likely insulin, did not match the amount of food ingested, or the level of exercise a patient performed was too much for the amount of food ingested and the amount of medication taken. But often, teasing out the exact triggers can be a challenge.

Table 1 provides a checklist of potential causes of hypoglycemia. HCPs may need to think like a crime scene investigator to uncover the causes and contributing factors that have led to a hypoglycemic event. Allowing individuals with diabetes and their family to tell their story about a hypoglycemic event may allow HCPs to uncover a need not only for medication changes, but also for changes in patients' behavioral responses to hypoglycemia. Empowering individuals to have more control over such situations will also help reduce the anxiety and fear often associated with hypoglycemia.

**Taking Time to Hear and Assess the Story of Hypoglycemia**

Probing patients with pertinent questions will help create an accurate understanding of the context of reported hypoglycemia. This can also reduce misunderstandings between patients and providers and provide

**Table 1. Checklist for Potential Causes of Hypoglycemia**

<p><b>Excessive Insulin or Insulin Secretagogue Dose</b></p> <ul style="list-style-type: none"> <li>• Dosage may need to be decreased or medication may need to be changed to a different type</li> <li>• Stacking insulin (i.e., administering mealtime boluses and/or hyperglycemia correction doses without accounting for the continuing effect of the previous dose)</li> </ul>
<p><b>Medication Administration Issues</b></p> <ul style="list-style-type: none"> <li>• Visual deficits leading to incorrect dosing of medication or insulin</li> <li>• Injection site issues                             <ul style="list-style-type: none"> <li>◦ Injecting insulin intramuscularly rather than subcutaneously</li> <li>◦ Injecting into lipohypertrophy</li> </ul> </li> <li>• Memory or distraction issues                             <ul style="list-style-type: none"> <li>◦ Taking the medication or insulin dose twice</li> <li>◦ Accidentally taking rapid-acting insulin instead of long-acting insulin</li> </ul> </li> <li>• Sub-optimal timing of insulin in relation to meals                             <ul style="list-style-type: none"> <li>◦ Taking rapid-acting insulin too far in advance of eating a meal or too long after a meal</li> </ul> </li> </ul>
<p><b>Decreased Exogenous Glucose Delivery</b></p> <ul style="list-style-type: none"> <li>• Missed or delayed meals</li> <li>• Miscalculated carbohydrate content</li> </ul>
<p><b>Decreased Endogenous Glucose Production</b></p> <ul style="list-style-type: none"> <li>• Alcohol ingestion</li> <li>• Renal failure or progression of renal disease</li> </ul>
<p><b>Increased Glucose Utilization</b></p> <ul style="list-style-type: none"> <li>• During or after increased physical activity</li> </ul>
<p><b>Increased Insulin Sensitivity</b></p> <ul style="list-style-type: none"> <li>• Weight loss</li> <li>• Insulin sensitizers such as metformin or pioglitazone when used in combination with insulin or sulfonylurea</li> <li>• During or after increased physical activity</li> </ul>
<p><b>Decreased Insulin Clearance</b></p> <ul style="list-style-type: none"> <li>• Declining renal function</li> </ul>
<p><b>Other Considerations</b></p> <ul style="list-style-type: none"> <li>• First trimester of pregnancy</li> <li>• Gastroparesis</li> <li>• Uncontrolled hypothyroidism</li> <li>• Advancing age</li> <li>• Intentional hypoglycemia (insulin overdose)</li> </ul>

education opportunities about skills or concepts that may seem basic to providers but can be challenging for patients.

When patients report that they have been experiencing low blood glucose, it is important to define hypoglycemia together. What do patients consider to be a low blood

glucose level? Is this based solely on feelings or have they been able to actually check their blood glucose at the moment of symptoms?

If self-monitoring of blood glucose (SMBG) records are available, at what point or level of blood glucose do individuals start to experience symptoms of hypoglycemia?

People with consistently high blood glucose levels will feel hypoglycemic at blood glucose levels higher than the normal range, whereas those with tight glycemic control may feel hypoglycemic at lower levels.<sup>7</sup>

Fear of these feelings associated with low blood glucose may prevent people with poorly controlled diabetes from taking their recommended doses of insulin or oral hypoglycemic medications even when their blood glucose levels never dropped to < 70 mg/dl while they were taking the recommended doses. On the other hand, decreased awareness of blood glucose dropping to < 60 mg/dl may prevent individuals from treating hypoglycemia before they lose neurological functioning or consciousness. Discussing these concepts with patients provides practical motivation and support for the role of SMBG in medication adjustment and safety.

Another area worthy of inquiry is patients' actions leading up to hypoglycemic events. It may seem obvious that changes in food choices, physical activity, or medication can produce hypoglycemia, but letting patients verbalize their patterns or changes in patterns can allow them to discover this for themselves.

Eating a smaller meal or one containing less carbohydrate than normal may result in a low postprandial blood glucose level. If changes in food choices lead to hypoglycemic events, patients likely did not do this on purpose. Have they been less hungry lately, or are they trying to lose weight? Has there been a change in their oral health? Many individuals do not understand the complexity of factors affecting postprandial glucose levels or are not able to consistently identify a low-carbohydrate or high-carbohydrate meal or to accurately estimate the number of calories in their meals.

For patients who are doing basic carbohydrate counting, explore the potential impact of the presence or absence of protein and fat in meals. These individuals may not recognize or may easily forget the role of protein and fat because they are concentrating more closely on carbohydrates.

For patients who are counting calories or using some overall means of portion control, explore the impact of significant changes in carbohydrate content and assess their ability to identify foods that are rich in carbohydrates. These individuals may not understand the importance of carbohydrate budgeting. In these discussions, providers may find patients to be at a point of readiness to be referred to a registered dietitian or certified diabetes educator for more nutrition education.

Changes in physical activity that can lead to hypoglycemia can include more than just intentional exercise. Particularly for people who are usually sedentary, an increase in overall energy and stamina that leads to doing more errands, gardening, or housework than normal may result in hypoglycemia. In contrast, athletes with diabetes who have temporary periods of two-a-day practices might need help learning how to adjust their

medication to deal with the increase in insulin sensitivity and glucose uptake that results from increased exercise.

Asking open-ended questions about the timing and dosing of medication or asking patients to demonstrate or describe their injection technique also may reveal potential causes of hypoglycemia.

Finally, it is important to ask exactly how patients treat low blood glucose. This question often reveals a tendency to consume more than the recommended 15–20 g of carbohydrate or may uncover a misunderstanding of what types of foods and substances will most quickly raise the blood glucose level. Table 2 reviews the recommended treatment guidelines for hypoglycemia.

Discussing patients' knowledge of food choices, physical activity, and medication can help prevent future hypoglycemia and allow providers to best determine any necessary changes in medication and identify education needs.

### Investigating the Other Causes of Hypoglycemia and Managing the Risks

#### Insulin injection sites

Lipohypertrophy is a buildup of fat at the injection site. Injecting insulin

**Table 2. Hypoglycemia Treatment**

**Rule of 15s for hypoglycemia treatment:**

- Check blood glucose level if possible
- Treat with 15–20 g of carbohydrate (e.g., 3–4 glucose tabs, glucose gel, 1/3 to 1/2 cup of juice, 6 oz of regular soda, 1 cup of milk)
- Recheck blood glucose level 15 minutes later
- Re-treat with above recommendation if blood glucose is not > 70 mg/dl

**Treatment for severe hypoglycemia:**

- Administer glucagon intramuscularly or subcutaneously
  - If patient is ≤ 5 years of age, administer 0.5 mg
  - If patient is > 5 years of age, administer 1 mg
- Follow with clear liquid soda and snack

into lipohypertrophy usually causes impaired absorption of insulin.<sup>9</sup> HCPs and patients rely on the time action of insulin to match carbohydrate intake and correct hyperglycemia. However, injecting into sites of lipohypertrophy can result in erratic and unexplained fluctuations in blood glucose.

When advising patients to rotate to new injection sites, HCPs should note the need for caution. Because insulin injected into a fresh site likely will be absorbed more efficiently, doses may need to be decreased.

Regular rotation of insulin injection sites may prevent lipohypertrophy from occurring. Keep in mind that some patients, especially children, may be hesitant to inject in areas other than one with lipohypertrophy because they report that area is less sensitive to injections.

#### **Alcohol intake**

Many alcohol-containing drinks contain carbohydrate and can cause initial hyperglycemia. However, alcohol also inhibits gluconeogenesis, which becomes the main source of endogenous glucose about 8 hours after a meal. Therefore, there is increased risk of hypoglycemia the morning after significant alcohol intake if there has not been food intake. Alcohol consumption can also interfere with the ability to feel hypoglycemia symptoms.<sup>10</sup>

For patients whose blood glucose is well controlled, the ADA guidelines for alcohol intake suggest a maximum of one to two drinks per day, consumed with food. Close monitoring of blood glucose for the next 10–20 hours may be beneficial.

#### **Decreased renal function**

Insulin and sulfonylurea clearance is decreased with impaired hepatic or renal function. Decreasing the dosages of some anti-hyperglycemic

medications and avoiding others may be necessary.

Of the oral agents, sulfonylureas are more likely to cause hypoglycemia. Glimepiride may be a safer choice than glyburide or glipizide in elderly patients and those with renal insufficiency because it is completely metabolized by the liver; cytochrome P450 reduces it to essentially inactive metabolites that are eliminated renally and fecally.<sup>11</sup> Lower doses likely still will be necessary with renal insufficiency.

As kidney function declines, exogenous insulin has a longer duration and is more unpredictable in its action, and the contribution of glucose from the kidney through gluconeogenesis is reduced.<sup>12,13</sup> Using insulin analogs, employing the use of multiple daily insulin dose regimens, and/or lowering insulin doses may aid in decreasing the risk of hypoglycemia.

#### **Gastroparesis considerations**

Patients who have had diabetes for many years or who have had poor control are at risk for autonomic neuropathy, including gastroparesis, or slow gastric emptying. It is thought that delayed food absorption increases the risk of hypoglycemia, although evidence is lacking. Intercurrent gastrointestinal problems such as gastroenteritis or celiac disease can also be causes of altered food absorption.<sup>10</sup>

Medications such as metoclopramide or erythromycin are used to increase gastric emptying time. Giving mealtime insulin after meals or using an extended bolus on an insulin pump may also help to prevent potential hypoglycemia related to delayed gastric emptying.

#### **Hypothyroidism effects**

Hypothyroidism slows the absorption of glucose through the gastrointestinal tract, reduces peripheral tissue

glucose uptake, and decreases gluconeogenesis. For people with diabetes, this can cause increased episodes of hypoglycemia. Measuring the level of thyroid-stimulating hormone is the most accurate method of evaluating primary hypothyroidism. As hypothyroidism is treated, an increase in insulin dose will likely be needed to meet the increased metabolic need.<sup>14</sup> Subclinical hypothyroidism has also been associated with an increased risk of symptomatic hypoglycemia.<sup>15</sup>

#### **Age factors**

The risk of severe hypoglycemia increases with age. Slowed counter-regulatory hormones, erratic food intake, and slowed intestinal absorption place older adults at higher risk of hypoglycemia.<sup>16</sup> Close attention to renal function, weight, and nutrition status may decrease the incidence of hypoglycemia in this population.

#### **Pregnancy-related hypoglycemia**

The incidence of mild and severe hypoglycemia is highest between 8 and 16 weeks' gestation in type 1 diabetes. Severe hypoglycemia in early pregnancy is three times more frequent than during preconception.<sup>17</sup> If unexplained or frequent hypoglycemia is occurring in a female of child-bearing age, HCPs should consider pregnancy as a possible cause of the hypoglycemia. Providing preconception counseling, including information about a potential increase in hypoglycemia early in pregnancy, may help reduce the incidence of hypoglycemia for women planning to become pregnant.

#### **Intentional hypoglycemia**

Intentional insulin overdose is thought to be relatively rare, but the actual prevalence is difficult to measure. A common method used to estimate the number of deliberate insulin overdoses is to analyze data from regional poison control

**Table 3. Diabetes Education Resources**

- ADA-recognized education programs  
<http://professional.diabetes.org/Recognition.aspx?typ=15&cid=84040> or call 1-800-DIABETES
- American Dietetic Association  
<http://www.eatright.org/programs/rdfinder>
- American Association of Diabetes Educators  
<http://www.diabeteseducator.org/ProfessionalResources/accred/Programs.html>

centers. In the 2005 annual report of the American Association of Poison Control Centers, only 3,934 of the 2,424,180 inquiries (0.16%) reported drug exposures involving insulin.

Although rare, most cases of insulin overdose reported to poison control centers have occurred during suicide attempts.<sup>18</sup> Depression is a common comorbidity of diabetes. HCPs who are unable to identify other reasons for persistent hypoglycemia may not be able to rule out intentional induction of hypoglycemia. Patients who are suspected of intentionally inducing hypoglycemia should be referred to a behaviorist for evaluation and treatment.

### Strategies to Reduce the Incidence of Hypoglycemia

#### Providing education for empowerment

Individuals with diabetes (and, ideally, their care partners) who have received diabetes self-management education should have a better understanding of how their medication, meal plan, and physical activity interact to achieve optimal glucose control while limiting hypoglycemia. They also will be better equipped to prevent and treat hypoglycemia should it occur.

HCPs should help individuals who have not had an opportunity to work with a diabetes educator or dietitian to identify educational resources in their area. Table 3 provides a list of resources for locating local diabetes educators and dietitians. Patients who have not had a recent diabetes education update may benefit from a refresher course.

Hypoglycemia education includes not only appropriate treatment and prevention, but also driving precautions, including performing SMBG before driving and frequently while driving for individuals who are prone to hypoglycemia. People with diabetes also should keep glucose tabs, gel, or other appropriate oral treatment options in their vehicle. Encouraging individuals to wear a medical identification listing diabetes and any other diagnoses they may have is also important.

#### Performing SMBG and reviewing results

Using a pattern-management approach for reviewing SMBG data will allow individuals with diabetes and their HCPs to adjust medications to better match food intake and physical activity. Reviewing SMBG results that include fasting, postprandial, and nocturnal test results will allow HCPs to craft a more physiological medication regimen for patients. SMBG also allows individuals to take appropriate preventive and follow-up actions related to hypoglycemia.

Today, the use of continuous glucose monitoring (CGM) systems can also help to limit hypoglycemia, especially in those who have frequent episodes with hypoglycemia unawareness and nocturnal hypoglycemia. HCPs may order a diagnostic CGM study to determine whether nocturnal hypoglycemia is occurring and to better identify patterns of hyperglycemia and hypoglycemia around the clock. An increasing number of individuals with insulin-

requiring diabetes are wearing CGM sensors as a part of their routine diabetes management.

#### Providing patients with Blood Glucose Awareness Training

Blood Glucose Awareness Training should be considered for patients with recurrent, severe hypoglycemia.<sup>19</sup> Hypoglycemia education should also include awareness that having severe hypoglycemia once increases the risk of having another severe episode for up to 6 months.<sup>20</sup> Glucose targets likely will need to be raised for the next 2–3 weeks to prevent hypoglycemia recurrence.

#### Conclusion

Hypoglycemia can be a limiting factor to optimal diabetes control. However, the risk of hypoglycemia can be minimized through adequate diabetes self-management education, SMBG, and individualization of medication regimens employing physiological insulin replacement and appropriate medication management.

HCPs' careful consideration of all potential factors associated with hypoglycemia will help patients reduce their hypoglycemia risk and achieve optimal glycemic control, thereby reducing their risk of long-term diabetes complications. Reducing the risks of hypoglycemia and empowering individuals and their families to prevent and treat it appropriately will ultimately help to reduce patients' fear of hypoglycemia and could result in improved diabetes control and quality of life.

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