The Diabetes Treatment Trap: Hypoglycemia

Michael J. Fowler, MD

Editor's note: *This article is the fifth in an eight-part series reviewing the fundamentals of diabetes care for physicians in training. This series is an updated adaptation of a 12-part series published in* Clinical Diabetes *between 2006 and 2009. The previous series, and earlier installments of this one, can be found online at the journal Web site (http://clinical.diabetesjournals.org).*

One of the ethical pillars of medical treatment has always been to "do no harm." Treating patients with diabetes medications, however, carries a significant risk of inflicting harm and injury by causing hypoglycemia. Were it not for this potential adverse reaction, diabetes treatment would be considerably easier for both patients and providers.

Such treatments frequently involve augmenting insulin effects directly (injected insulin) or indirectly (increasing insulin release from the pancreatic β-cells, increasing insulin sensitivity, and/or inhibiting hepatic glucose production). Whenever glucose homeostasis is altered, hypoglycemia is always a potential side effect to therapy and, in fact, is one of the most common adverse reactions in diabetes treatment.

It is important, therefore, to be able to identify, treat, and also avoid the hypoglycemic complications of diabetes therapy. Such complications may even be life-threatening and resistant to initial therapy. Therefore, physicians who prescribe potent diabetes medications such as insulin must be able to identify the causes of such adverse reactions and arrest such complications before they progress.

Hypoglycemia Mechanisms

Hypoglycemia is in many ways the Achilles heel of diabetes treatment. Medical authors have astutely noted that hypoglycemia is the "limiting factor" in the treatment of diabetes.[1–3] Reduction of glucose levels in patients with either type 1 or type 2 diabetes has been shown to decrease the risks of kidney, nerve, and retinal injury. Lower glucose levels are also associated with a reduction in cardiovascular disease in patients with type 1 diabetes. Were it not for the development of hypoglycemia, all patients with diabetes could conceivably control their diabetes with ease using high doses of oral medications or insulin.

Such is not the case, however. Treatment of diabetes, especially intensive treatment, carries a significant risk of lowering blood glucose levels excessively and causing hypoglycemia. Severe hypoglycemia is usually considered to be an episode of hypoglycemia in which a patient requires assistance from another person.[1,2] More intensive glucose control is associated with a decrease in microvascular complications of diabetes but also significantly increases the risk of hypoglycemia, and sometimes severe hypoglycemia.[4,5] The risk of hypoglycemia is greater with lower average glucose levels.[1, 3–5] Thus, patients who are more compliant or astute in using their medication and lowering their glucose levels may be the ones at greater risk to be harmed from hypoglycemia.

In discussing hypoglycemia, it is important to first understand the body's normal response to low glucose levels. In nondiabetic individuals and in those with diabetes who have intact response mechanisms, the response to hypoglycemia typically progresses in an orderly and escalating manner.

The first barrier in protecting against hypoglycemia is decreased insulin release, primarily determined by the glucose concentration surrounding the pancreatic β-cells (although other factors may be involved). Normally, high glucose concentrations elicit high levels of insulin release from the pancreas. Conversely, insulin secretion declines and is quite low as glucose declines to low-normal levels, around 80 mg/dl in venous blood. Low insulin levels stimulate increases in hepatic and renal glucose production to counteract further decrease in glucose levels.

The human neuroendocrine system serves as the second barrier of protection against hypoglycemia. If glucose continues to decline, glucagon is released from the pancreatic α-cells, and epinephrine is released from the adrenal medullae at mild levels of hypoglycemia

(around 65–70 mg/dl). Glucagon raises glucose levels by stimulating hepatic glucose production via glycogenolysis and gluconeogenesis. Epinephrine release from the adrenal medullae also stimulates hepatic and renal glucose production and decreases glucose utilization by peripheral tissues.

Activation of the sympathoadrenal system and other neuroendocrine signals can also produce tachycardia, nervousness, anxiousness, and vasoconstriction. These are the signals most patients learn to recognize as hypoglycemia. There is also increased release of cortisol and growth hormone, both of which indirectly lead to higher glucose concentrations over longer periods of time and are less important in acute recovery from hypoglycemia.

If glucose levels continue to decline into the mid-50 mg/dl range, patients typically develop neuroglycopenic symptoms. These symptoms, which arise from insufficient glucose delivery to the brain and other neural tissues, usually include warmth and cognitive dysfunction such as confusion and lethargy but can also progress to more serious impairment such as seizures and loss of consciousness. The degree of the body's response to hypoglycemia depends on the extent of the glucose drop rather than the rate of decline.[1,2]

One potential concern regarding hypoglycemia, especially severe hypoglycemia, is the risk of neurological injury. Fortunately, permanent neurological injury from hypoglycemia is rare. In primate models, glucose concentrations of < 20 mg/dl for several hours were necessary to produce permanent neurological injury.[6]

Patients with either type 1 or type 2 diabetes may develop hypoglycemia during their course of treatment as a side effect to essentially any diabetes medication. Patients with type 1 diabetes are particularly susceptible to hypoglycemia for several reasons. Using exogenous insulin to regulate glucose levels precludes the body's initial mechanism to prevent hypoglycemia: decreased insulin production. Normally, insulin production (especially postprandially) is a very closely controlled process in which the body constantly monitors its glucose level. In contrast, treatment of hyperglycemia with injected insulin lacks feedback mechanisms and the ability to adjust insulin release on a minute-to-minute basis, as performed by the normally functioning human body.

Put into context, patients are attempting to precisely match the rate of insulin entry into the bloodstream with the rate of glucose entry into the bloodstream using subcutaneous insulin injections. This can be difficult to achieve even in research settings. Moreover, patients with type 1 diabetes are absolutely insulin deficient and tend to be more insulin sensitive than patients with type 2 diabetes, so there may be less room for error in insulin dosing for those with type 1 diabetes. This scenario presents a daunting challenge, to say the least.

To further exacerbate susceptibility to hypoglycemia, patients with type 1 diabetes also experience impaired glucagon release in response to hypoglycemia through unknown mechanisms. Normally, glucagon release appears to be mediated through a complex interaction of pancreatic islet arterial glucose level, neurological input, and local insulin secretion from β-cells. But the relative importance of these factors is not clearly defined.

Additionally, release of epinephrine is reduced in patients with established type 1 diabetes, possibly because of exposure to hypoglycemia. As previously stated, most patients learn to recognize hypoglycemia through the symptoms elicited through epinephrine, so impaired epinephrine response can lead to both impaired recovery and impaired awareness of hypoglycemia. Blunted epinephrine release may be further exacerbated in patients with autonomic dysfunction. Patients with type 1 diabetes require greater degrees of hypoglycemia to signal epinephrine release. Combining these factors into the clinical scenario of type 1 diabetes yields a breached second barrier against hypoglycemia and a high susceptibility to hypoglycemia.[1,2]

Patients with type 2 diabetes exhibit lower propensity to hypoglycemia, at least early in their disease course. Initially, they do not appear to exhibit impaired glucagon release. As insulin deficiency progresses, however, they also exhibit impaired glucagon release similar to that seen in type 1 diabetes. Epinephrine release in response to hypoglycemia is also impaired in patients with type 2 diabetes who have experienced antecedent hypoglycemia. As insulin deficiency progresses in type 2 diabetes, so does its clinical resemblance to type 1 diabetes with respect to hypoglycemia.[1,2,7]

Hypoglycemia Unawareness

When patients experience impairment of epinephrine and other responses to hypoglycemia, their awareness of, and therefore their ability to defend against, hypoglycemia is compromised. Such is the case in many patients with longstanding diabetes, especially those with type 1 diabetes. As described previously, patients' initial warning of hypoglycemia is frequently the nervousness, anxiousness, and tremulousness that are direct results of epinephrine release. Without these adrenergic symptoms, many patients do not develop warning of hypoglycemia until they develop neuroglycopenic symptoms,

which can be especially dangerous in individuals who are operating motor vehicles or machinery or are in other precarious situations. Avoidance of hypoglycemia for several weeks may help improve hypoglycemia awareness.[2]

Treatment of Hypoglycemia

Teaching patients to recognize and treat hypoglycemia is a key component of diabetes care. When patients detect the above symptoms, they should perform a fingerstick glucose measurement. If the reading is < 70 mg/dl, they should consume 15–20 g carbohydrate. Examples include 6 oz of orange or apple juice, three to four commercially available glucose tablets, or other forms of easily obtainable carbohydrate. It should be noted that protein consumption is not an effective treatment of hypoglycemia, and consumption of sweet snacks that are also high in fat (such as ice cream or icing) may delay absorption of carbohydrate. Pure glucose is the preferred treatment.

Patients should recheck their glucose again in 15 minutes to confirm that it has returned to normal. If their glucose is still low, they should consume another 15–20 g carbohydrate.

It is important to remember that ongoing action of injected insulin or insulin secretagogues may cause recurrent hypoglycemia after an initial recovery, so patients should be cautious in this regard.[8] Patients should, however, avoid consuming very large amounts of carbohydrate because this may be associated with considerable rebound hyperglycemia.

Patients experiencing severe hypoglycemia become confused, combative, lethargic, or unconsciousness and therefore require the assistance of another individual. In such an event, an emergency glucagon kit should be used to raise glucose levels. Glucagon kits are commercially available and may be administered by patients' family, friends, or caregivers. Patients who are at significant risk of major hypoglycemia should have glucagon kits, and their family and caregivers should be instructed in their safe use.[8]

Hypoglycemia Prevention

Patients who experience severe hypoglycemia because of hypoglycemia unawareness may regain some hypoglycemia awareness if they adhere to higher glucose targets and avoid hypoglycemia for several weeks.[2] Continuous glucose monitors, which are now commercially available, may also help to limit glucose excursions.[9] However, they have not yet been definitively shown to decrease risk of severe hypoglycemia.

Evaluating the cause of hypoglycemia is perhaps just as important as treating hypoglycemia when it occurs. Patients treated for hypoglycemia may experience drops in glucose levels from increased activity, decreased appetite, incorrect administration of insulin or oral medications, or other causes. Recurrent hypoglycemia may be an indicator of adrenal insufficiency, especially in patients with preexisting autoimmune disease such as type 1 diabetes. A careful history should be taken to analyze the cause and pattern of hypoglycemia and adjust therapy or perform further evaluation that can prevent future hypoglycemic episodes.

Patients should also be educated to be cognizant of situations that place them at increased risk of hypoglycemia, such as instances where they have increased exercise or physical activity. They may decrease their diabetes therapy preemptively or consume extra carbohydrate in such situations to prevent hypoglycemia before it occurs. Patients at risk for significant hypoglycemia should also be taught to check their glucose level before driving or operating equipment such as lawnmowers or workplace machinery.

Use of new long-acting basal insulin analogs may help stabilize glucose levels and thereby reduce the risk of hypoglycemia, especially minor hypoglycemia.[10,11] Switching patients from conventional regimens (regular and NPH insulin) to basal-bolus insulin therapy with insulin analogs may decrease their risk of minor hypoglycemia. It is important to also note that not all studies have borne out this relationship. Furthermore, the risk of major hypoglycemia has not differed in several studies comparing new insulin analogs and conventional insulin regimens.[11,12] Insulin analogs are also considerably more expensive than regular and NPH insulin.

Insulin pump therapy offers the advantage of delivering very small doses of insulin and administering variable basal insulin doses. As a result, pump therapy may carry a lower risk of hypoglycemia in patients with type 1 diabetes. Several studies have suggested that the risk of hypoglycemia is reduced using insulin pump therapy,[11] but it should be noted that insulin pumps can be quite labor-intensive and are not appropriate for all patients. They are also expensive, costing several thousand dollars for the pump itself and then additionally for monthly supplies.[11,13]

Summary

The goal of diabetes therapy is to normalize glucose levels without lowering them excessively. Virtually any diabetes treatment, however, is also capable of causing hypoglycemia.

Hypoglycemia is a potentially life-threatening complication of diabetes therapy and is a significant cause of morbidity and mortality, especially in insulin-treated patients.

As a result, physicians must be cognizant of its occurrence. Risks of hypoglycemia should be weighed heavily during initiation of or adjustment in diabetes treatment regimens.

Patients should be taught not only to recognize the signs and symptoms of hypoglycemia and to treat it when it occurs, but also to prevent it. Such precautions should allow medical practitioners to optimize their patients' glucose control while minimizing their risk of harm from mild or severe hypoglycemia.

REFERENCES

[1]Cryer PE: Hypoglycaemia: the limiting factor in the glycaemic management of type I and type II diabetes. *Diabetologia* 45:937–948, 2002

[2]Cryer PE, Davis SN, Shamoon H: Hypoglycemia in diabetes. *Diabetes Care* 26:1902–1912, 2003

[3]Havlin CE, Cryer PE: Hypoglycemia: the limiting factor in the management of insulin-dependent diabetes mellitus. *Diabetes Educ* 14:407–411, 1988

[4]DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993

[5]U.K. Prospectoive Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998

[6]Cryer PE: Hypoglycemia, functional brain failure, and brain death. *J Clin Invest* 117:868–870, 2007

[7]Segel SA, Paramore DS, Cryer PE: Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 51:724–733, 2002

[8]American Diabetes Association: Standards of medical care in diabetes—2010. *Diabetes Care* 33 (Suppl. 1):S11–S61, 2010

[9]Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S, Jovanovic L: Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. *Diabetes Care* 29:44–50, 2006

[10]Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P, Landin-Olsson M, Hylleberg B, Lang H, Draeger E: Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. *Diabetes Care* 27:1081–1087, 2004

[11]Pickup JC, Renard E: Long-acting insulin analogs versus insulin pump therapy for the treatment of type 1 and type 2 diabetes. *Diabetes Care* 31 (Suppl. 2):S140–S145, 2008

[12]Raskin P, Klaff L, Bergenstal R, Halle JP, Donley D, Mecca T: A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. *Diabetes Care* 23:1666–1671, 2000

[13]Hunger-Dathe W, Braun A, Muller UA, Schiel R, Femerling M, Risse A: Insulin pump therapy in patients with type 1 diabetes mellitus: results of the Nationwide Quality Circle in Germany (ASD) 1999–2000. *Exp Clin Endocrinol Diabetes* 111:428–434, 2003

Michael J. Fowler, MD, is an assistant professor of medicine in the Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt Eskind Diabetes Clinic, at Vanderbilt University Medical Center in Nashville, Tenn. He is also an associate editor of Clinical Diabetes.