Hypoglycemia

Michael J. Fowler, MD

Editor's note: This article is the 8th in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the Clinical Diabetes *website (http://clinical.diabetesjournals.org).*

One of the first tenants of medical practice is 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 side effect, diabetes treatment would be considerably easier.

Many treatments frequently involve augmenting insulin effects directly (injected insulin) or indirectly (increasing insulin release from the pancreatic β-cells, increasing insulin sensitivity, or inhibiting hepatic glucose production). When endogenous insulin levels are 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 mild and severe hypoglycemic complications of diabetes therapy. Such complications may be life-threatening and resistant to initial therapy; therefore, it is important for physicians who prescribe potent diabetes medications such as insulin to be able to identify causes of such adverse reactions and arrest them 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 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 reduction in cardiovascular disease in patients with type 1 diabetes. Were it not for the development of hypoglycemia, every patient with diabetes could conceivably control their diabetes with greater ease using high doses of oral medications or insulin.

Such is not the case, however. Treatment of diabetes, especially intensive treatment, brings the 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 it also significantly increases the risk of hypoglycemia, sometimes severe.[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 to lower their glucose levels may be the ones at greatest 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 or those with diabetes who have intact response mechanisms, the response to hypoglycemia typically progresses in an orderly and escalating manner.

The first barrier of protection against hypoglycemia is decreased insulin release, primarily determined by 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 normal pancreas. Conversely, insulin secretion declines and is quite low as the individuals' 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 β-cells, and epinephrine is released by the adrenal medullae at mild levels of hypoglycemia (~ 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 cortisol and growth hormone release; both these hormones 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 are symptoms that arise from insufficient glucose delivery to the brain and other neural tissues and usually include symptoms such as warmth and cognitive dysfunction such as confusion and lethargy. They can also progress to more serious impairment, such as seizure 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 if severe, is the risk of neurological injury. Permanent neurological injury from hypoglycemia is, fortunately, rare. In primate models, glucose concentrations of < 20 mg/dl for several hours were necessary for production of permanent neurological injury.[6]

Patients with either type 1 or type 2 diabetes may develop hypoglycemia during the course of treatment with virtually all diabetes medications. 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 with constant monitoring of glucose levels by the body. In contrast, treatment of hyperglycemia with insulin lacks feedback mechanisms and the ability to adjust insulin release on a minute-to-minute basis as performed by the 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, a task that can be difficult even in research settings. Furthermore, 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 their insulin dosing. This scenario presents a daunting challenge.

To further exacerbate susceptibility to hypoglycemia, patients with type 1 diabetes also experience impaired glucagon release in response to hypoglycemia through uncertain 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 previous 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 a lower propensity to hypoglycemia, at least early in their disease course. Initially, they do not appear to exhibit impaired glucagon release in response to hypoglycemia. 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 in respect to hypoglycemia.[1,2,7]

Hypoglycemia Unawareness

When patients experience impairment of epinephrine and other responses to hypoglycemia, their awareness of and, therefore, ability to defend against hypoglycemia is compromised. Such is the case in many patients with longstanding diabetes, especially 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 have warnings 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 a patient to recognize and treat hypoglycemia is a key component of diabetes care. When patients detect the symptoms discussed above, they should perform a blood glucose test. If the reading is < 70 mg/dl, they should consume 15–20 g of carbohydrate. Examples include 4–6 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 a sweet snack that is 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 blood 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 of 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 consumption of very large amounts of carbohydrate because this may be associated with considerable rebound hyperglycemia.

During severe hypoglycemia, individuals become confused, combative, lethargic, or unconscious 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 proper use.[8]

Hypoglycemia Prevention

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

Perhaps just as important as the treatment of hypoglycemia is evaluation to identify the cause of hypoglycemia. Patients treated for hypoglycemia may experience drops in glucose levels because of increased physical 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 a pre-existing autoimmune disease, such as type 1 diabetes. A careful history should be taken to analyze the cause and pattern of hypoglycemia to adjust therapy or perform further evaluation that can prevent future hypoglycemia.

Patients should also be educated to be cognizant of situations that place them at increased risk of hypoglycemia, such as 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 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 that use regular and NPH insulins to the more physiological 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, and, 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 using regular and NPH insulin.

Insulin pump therapy possesses the advantage of delivering both very small doses of insulin and variable basal doses. As a result, it may provide a lower risk of hypoglycemia for 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]

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 very cognizant of its occurrence. Risks of hypoglycemia should be weighed heavily during initiation or adjustment of diabetes treatment regimens. Patients should be taught the signs, symptoms, and proper treatment of hypoglycemia, as well has how to prevent it. Such precautions should allow medical practitioners to optimize glucose control while minimizing the risk of harm to their patients from mild or severe hypoglycemia.

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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 an associate editor of Clinical Diabetes.