Defective Counterregulation and Hypoglycemia Unawareness in Diabetes

Mechanisms and Emerging Treatments

Candace M. Reno, PhD[a], Marina Litvin, MD[a], Amy L. Clark, DO[b], Simon J. Fisher, MD, PhD[a,c,*]

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• Hypoglycemia • Unawareness • Glucose • Diabetes • Counterregulation • Brain • Hypothalamus • Hypoglycemia-associated autonomic failure

KEY POINTS

- Hypoglycemia continues to be a major barrier to the achievement of long-term glucose control, causing recurrent morbidity in individuals with diabetes.
- Numerous sedulous research studies have begun to uncover the mechanisms by which the central nervous system responds and adapts to hypoglycemia.
- Understanding these mechanisms will undoubtedly lead to better management and therapies that reduce the risk for hypoglycemia, while still allowing patients to achieve the benefits associated with tight glycemic control.
- Given this pervasive barrier of hypoglycemia for the treatment of diabetes, physicians should discuss hypoglycemia prevention strategies with their patients, so they can have a better chance of achieving their goals of glucose control while avoiding the morbidity and mortality associated with hypoglycemia.

HYPOGLYCEMIA: THE CLINICAL PROBLEM

Poorly controlled diabetes is associated with vascular complications including renal failure, peripheral vascular disease, neuropathy, blindness, amputations, coronary artery disease, and stroke. Multiple large clinical trials have shown the benefits of intensifying glycemic control in preventing or delaying microvascular complications. These trials, however, consistently report significantly higher rates of hypoglycemia

[a] Division of Endocrinology, Metabolism & Lipid Research, Department of Medicine, Washington University, 660 South Euclid Avenue, St Louis, MO 63110, USA; [b] Division of Endocrinology and Diabetes, Department of Pediatrics, Washington University, 660 South Euclid Avenue, St Louis, MO 63110, USA; [c] Department of Cell Biology and Physiology, Washington University, 660 South Euclid Avenue, St Louis, MO 63110, USA
* Corresponding author. Division of Endocrinology, Metabolism & Lipid Research, Washington University in St Louis, Campus Box 8127, 660 South Euclid Avenue, St Louis, MO 63110.
E-mail address: sfisher@dom.wustl.edu

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in patients who intensify their glycemic control.[1–5] Thus, hypoglycemia becomes the limiting factor for blood-glucose management in patients with diabetes, and precludes the attainment of microvascular benefits associated with tight glycemic control.

INCIDENCE OF HYPOGLYCEMIA

Compared with earlier self-reported and glucometer-based studies, studies based on continuous glucose monitoring more accurately assess the true incidence of hypoglycemia. In reasonably well-controlled patients with type 1 diabetes (HbA1c 7.6%), biochemical hypoglycemia (<60 mg/dL) averaged a disconcertingly high 2.1 times per 24 hours.[6] Of note, even in the group of people who reported intact hypoglycemia awareness, biochemically confirmed hypoglycemia failed to elicit symptoms 62% of the time.[6] Thus, symptomatic hypoglycemia underestimates the true incidence of hypoglycemia, and hypoglycemia awareness is not an "all or none" phenomenon.

As discussed in this article, episodes of moderate hypoglycemia are not without clinical consequences. Recurrent episodes of moderate hypoglycemia can lead to decreased sympathoadrenal responses and decreased awareness of hypoglycemia, collectively termed hypoglycemia-associated autonomic failure (HAAF),[7] which leads to an increased risk of more frequent and more severe episodes of hypoglycemia.

SEVERE HYPOGLYCEMIA

Severe hypoglycemia is defined clinically as occurring when the patient requires assistance from another individual to correct hypoglycemia. For insulin-treated diabetic patients, severe hypoglycemia has a high prevalence (46% and 25%) and high incidence (3.2 and 0.7 episodes per person-year) for people with type 1 and type 2 diabetes, respectively.[8] Severe hypoglycemia is associated with excess morbidity and mortality[7]; it can alter brain structure[9] and cause brain damage,[10,11] cognitive dysfunction,[12,13] and even sudden death.[14] It is estimated that between 6% and 10% of patients with type 1 diabetes die from hypoglycemia.[15–17] The mechanism by which low glucose levels lead to sudden death has not been entirely worked out, but seems to be related to intensive sympathetic activation leading to fatal cardiac arrhythmias.[18,19]

THE COUNTERREGULATORY RESPONSE TO HYPOGLYCEMIA

Because the brain is continuously dependent on peripheral glucose for metabolism, robust counterregulatory mechanisms exist to rapidly increase blood-glucose levels to protect the body from the pathologic consequences of hypoglycemia. In the setting of absolute or relative hyperinsulinemia, the counterregulatory response (CRR) is normally initiated when glucose levels fall below 80 mg/dL. The CRR to hypoglycemia normally includes suppression of endogenous insulin secretion and increase the secretion of glucagon, catecholamines (epinephrine, norepinephrine), cortisol, and growth hormone, which together act to increase plasma glucose levels by stimulating hepatic glucose production and limiting the use of glucose in peripheral tissues (**Fig. 1**).

GLUCAGON RESPONSE TO HYPOGLYCEMIA

Normally as blood-glucose levels decrease, increased glucagon secretion from the pancreatic α cells and decreased insulin secretion are the primary counterregulatory mechanisms by which hepatic glucose production is increased. Insulin-deficient diabetes results in an acquired defect of the glucagon response.[20] Several mechanisms have been proposed to explain this phenomenon, including defective