



Primum Non Nocere: Refocusing Our Attention on Severe Hypoglycemia Prevention

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Severe hypoglycemia, defined as low blood glucose requiring assistance for recovery, is arguably the most dangerous complication of type 1 diabetes as it can result in permanent cognitive impairment, seizure, coma, accidents, and death (1,2). Since the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive intervention to normalize glucose prevents long-term complications but at the price of a threefold increase in the rate of severe hypoglycemia (3), hypoglycemia has been recognized as the major limitation to achieving tight glycemic control. Severe hypoglycemia remains prevalent among adults with type 1 diabetes, ranging from ~1.4% per year in the DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) follow-up cohort (4) to ~8% in the T1D Exchange clinic registry (5).

One of the greatest risk factors for severe hypoglycemia is impaired awareness of hypoglycemia (6), which increases risk up to sixfold (7,8). Hypoglycemia unawareness results from deficient counterregulation (9), where falling glucose fails to activate the autonomic nervous system to produce neuroglycopenic symptoms that normally help patients identify and respond to episodes (i.e., sweating, palpitations, hunger) (2). An estimated 20–25% of adults with type 1 diabetes have impaired hypoglycemia awareness (8),

which increases to more than 50% after 25 years of disease duration (10).

Screening for hypoglycemia unawareness to identify patients at increased risk of severe hypoglycemic events should be part of routine diabetes care. Self-identified impairment in awareness tends to agree with clinical evaluation (11). Therefore, hypoglycemia unawareness can be easily and effectively screened using multiple, self-administered methods (11). These range from single questions (i.e., “Do you know when your hypos are coming?” [7] and “Can you feel when you are low?” [12]) to longer assessments characterizing hypoglycemia exposure and the glycemic threshold for symptomatic response, as in the 8-item Clarke questionnaire (11), and problematic hypoglycemia with unawareness during wake and asleep, as in the recently developed 33-item Hypoglycaemia Awareness Questionnaire (HypoA-Q) (13).

Interventions for hypoglycemia unawareness include a range of behavioral and medical options. Avoiding hypoglycemia for at least several weeks may partially reverse hypoglycemia unawareness and reduce risk of future episodes (1). Therefore, patients with hypoglycemia and unawareness may be advised to raise their glycemic and HbA_{1c} targets (1,2). Diabetes technology can play a role,

including continuous subcutaneous insulin infusion (CSII) to optimize insulin delivery, continuous glucose monitoring (CGM) to give technological awareness in the absence of symptoms (14), or the combination of the two in newer sensor-augmented insulin pumps with automated low-glucose suspend to prevent hypoglycemia (14). For patients who are refractory to medical treatment, human islet cell transplantation has been shown to mitigate severe hypoglycemia over 2 years (15), although this approach carries additional risks, expenses, and uncertain long-term benefit (16).

Aside from medical management, structured or hypoglycemia-specific education programs that aim to prevent hypoglycemia are recommended for all patients with severe hypoglycemia or hypoglycemia unawareness (14). In randomized trials, psychoeducational programs that incorporate increased education, identification of personal risk factors, and behavior change support have improved hypoglycemia unawareness and reduced the incidence of both nonsevere and severe hypoglycemia over short periods of follow-up (17,18) and extending up to 1 year (19).

The study by Little et al. (20) in this issue of *Diabetes Care* is an elegant addition to existing data on the potential of

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See accompanying article, p. 1600.

Hyperglycemia is, after all, only part of the puzzle in diabetes management. Long-term complications are decreasing across the population with improved interventions and their implementation (24). To this end, it is essential to shift our historical obsession with hyperglycemia and its long-term complications to equally emphasize the disabling, distressing, and potentially fatal near-term complication of our treatments, namely severe hypoglycemia. The American Diabetes Association (ADA) should assemble and expand current recommendations in the *Standards of Medical Care in Diabetes* with a dedicated chapter on both low-cost and technologically driven assessments for hypoglycemia unawareness and the prevention of severe hypoglycemia. The focus of such a chapter should be on implementation with an emphasis on individualization, patient autonomy, and overall well-being. The health care providers' first dictum is *primum non nocere*—above all, do no harm. ADA must refocus our attention on severe hypoglycemia as an iatrogenic and preventable complication of our interventions.

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