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Hypoglycemia

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ABSTRACT

Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment and is a major barrier to initiating or intensifying antihyperglycemic therapy in efforts to achieve better glycemic control. Therapy regimen and a history of hypoglycemia are the most important predictors of future events. Other risk factors include renal insufficiency, older age, and history of hypoglycemia-associated autonomic failure. Reported rates of hypoglycemia vary considerably among studies because of differences in study design, definitions used, and population included, among other factors. Although occurring more frequently in type 1 diabetes, hypoglycemia also is clinically important in type 2 diabetes. Symptoms experienced by patients vary among individuals, and many events remain undiagnosed. The incidence of severe events is unevenly distributed, with only a small proportion (~5%) of individuals accounting for >50% of events. Consequently, clinicians must be conscientious in obtaining thorough patient histories, because an accurate picture of the frequency and severity of hypoglycemic events is essential for optimal diabetes management. Severe hypoglycemia in particular is associated with an increased risk of mortality, impairments in cognitive function, and adverse effects on patients' quality of life. Economically, hypoglycemia burdens the healthcare system and adversely affects workplace productivity, particularly after a nocturnal event. Ongoing healthcare reform efforts will result in even more emphasis on reducing this side effect of diabetes treatment. Therefore, improving patients' self-management skills and selecting or modifying therapy to reduce the risk of hypoglycemia will increase in importance for clinicians and patients alike.

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Hypoglycemia is a common, potentially avoidable consequence of diabetes treatment and a major barrier to better metabolic control in type 1 and type 2 diabetes. It is a significant concern of primary care practitioners and patients when it comes to initiating or intensifying antihyperglycemic therapy.[1] Hypoglycemia can be defined in several ways: by plasma glucose values (biochemical definition), by symptoms (type and severity), and by time of day in which it occurs (daytime or nocturnal).[2] The literature is inconsistent in describing biochemical hypoglycemia, and these definitions may vary in clinical trials in inpatient versus outpatient settings; thus, an American Diabetes Association (ADA) workgroup has proposed 5 classifications (**Table 1**).[2] As Seaquist et al[2] have noted, the ADA standard of ≤70 mg/dL (3.9 mmol/L) is an alert value, intended to provide a margin of error for the limited accuracy of glucose monitoring devices at lower glucose levels. Because this value is above the threshold for symptoms, it allows sufficient time for corrective action to be taken.

It has been questioned whether the ADA standard is the most appropriate cutoff point for the biochemical definition of hypoglycemia because it is based on glucose-clamp studies, which measure arterialized venous samples, whereas it is capillary glucose, which tends to be approximately 15% lower than venous samples, that is typically measured in practice. Thus, it has been argued that in the absence of symptoms, a lower level (eg, ≤63 mg/dL [3.5 mmol/L]) should be used for biochemical definition.[3]

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Table 1 Definitions of Hypoglycemia[2]

Severe Hypoglycemia	Documented Symptomatic Hypoglycemia	Asymptomatic (Documented) Hypoglycemia	Probable Symptomatic Hypoglycemia	Pseudo-hypoglycemia
Requires assistance of a third party and is ameliorated by normalization of plasma glucose	Typical symptoms accompanied by measured plasma glucose ≤70 mg/dL	Measured plasma glucose ≤70 mg/dL but without typical symptoms	Typical symptoms responding to self-treatment but not confirmed by biochemical documentation but presumably caused by plasma glucose ≤70 mg/dL	Typical symptoms but with a measured plasma glucose greater than but approaching 70 mg/dL

With respect to symptomatic definitions, hypoglycemia may be self-treated (mild) or severe/major (ie, requiring assistance of a third party).[2] Symptoms can be divided into 2 broad groups: autonomic (eg, sweating, heart palpitations, shaking, dizziness, hunger) and neuroglycopenic (eg, confusion, drowsiness, speech difficulty, odd behavior, incoordination).[4,5] Unfortunately, the symptoms experienced are inconsistent between individuals, which complicates our efforts in identifying hypoglycemia and in counseling patients who experience these symptoms.[6] Furthermore, symptoms are not pathognomonic and can occur while a person is biochemically normoglycemic (pseudo-hypoglycemia) or when normalizing glucose levels in those patients with prolonged hyperglycemia.[7] Assessing the frequency of nocturnal hypoglycemia is challenging because of inconsistencies in defining the beginning and end of the nocturnal period in various studies. Furthermore, continuous glucose monitoring studies confirm that many episodes of hypoglycemia are not detected by patients with type 1 diabetes[8] and type 2 diabetes.[9]

FREQUENCY OF HYPOGLYCEMIA

Data from population-based studies confirm that hypoglycemia rates are higher in patients with type 1 diabetes than in those with type 2 diabetes. For example, in a random sample of 267 insulin-treated people, 94 with type 1 diabetes had a total of 336 hypoglycemic events (42.89 events per person-year), 9 of which were severe (1.15 events per person-year). By comparison, 173 people with type 2 diabetes experienced a total of 236 hypoglycemic events (16.37 events per person-year), 5 of which were severe (0.35 events per person-year).[10] Another review estimated that 7% to 25% of patients with type 2 diabetes using insulin experience at least 1 severe episode annually.[4] Hypoglycemia also is commonly reported in people with type 2 diabetes using oral medications.[4,11]

Nevertheless, it is important to recognize the limitations of making a broad generalization about the comparative incidence in type 1 diabetes versus type 2 diabetes in community populations or in randomized trials. Randomized trials may titrate patients more ambitiously, but exclude people with a high risk of severe hypoglycemia or hypoglycemia unawareness. If treated to a very tight glucose target, patients with type 2 diabetes conceivably could be at a similar risk to those with type 1 diabetes. In population statistics (in type 1 diabetes), the distribution of severe hypoglycemia is skewed, with a small proportion (5%) of individuals accounting for the majority (54%) of events.[12] It is critical that these patients be identified and case managed more proactively.

RISK FACTORS/BEHAVIORS PREDISPOSING TO HYPOGLYCEMIA

Antidiabetic therapies, individually and used in combination, vary substantially in their risk of hypoglycemia.[13-16] In one meta-analysis of intensification after failure of maximal metformin monotherapy, all noninsulin second-tier medications provided similar improvements in glycemic control, but were distinguishable by different rates of hypoglycemia (**Table 2**).[15]

Studies have identified numerous patient-level predictors of hypoglycemia. In type 1 diabetes, these include a history of hypoglycemia ($P = .006$) and co-prescribing of any oral drug ($P = .048$), whereas in insulin-treated type 2 diabetes, predictors included a history of hypoglycemia ($P < .0001$) and duration of insulin treatment ($P = .014$).[10] In a study of patients intensifying therapy because of insufficient control on 1 or 2 oral medications, after adjustment for confounding variables, the following factors were significant predictors: prior anamnestic (remembered) hypoglycemia (odds ratio [OR], 4.05; 95% confidence interval [CI], 3.04-5.39), preexistent retinopathy (OR, 3.27; 95% CI, 1.07-30.02), preexistent clinically relevant depression (OR, 1.81; 95% CI, 1.14-2.88), insulin use starting at baseline (OR, 2.99; 95% CI, 2.27-3.95), and blood glucose self-measurement (OR, 1.72; 95% CI, 1.23-2.41).[16] In type 2 diabetes, factors that have been reported to precede a severe hypoglycemic episode include a change in food intake, more vigorous exercise, increase in insulin dose, and cognitive impairment, among others.[13] Caffeine is an example of a commonly ingested substance that, by virtue of its potential to produce resting tremors and tachycardia, may enhance the intensity of warning symptoms, and thus increase the number of mild episodes reported.[17]