

Defining and Reporting Hypoglycemia in Diabetes

A report from the American Diabetes Association Workgroup on Hypoglycemia

AMERICAN DIABETES ASSOCIATION
WORKGROUP ON HYPOGLYCEMIA

Iatrogenic hypoglycemia causes recurrent morbidity in most people with type 1 diabetes and in many with type 2 diabetes and is sometimes fatal. It also impairs defenses against subsequent hypoglycemia. Furthermore, the barrier of hypoglycemia precludes maintenance of euglycemia over a lifetime of diabetes; thus, full realization of the benefits of glycemic control is rarely achieved. Therefore, hypoglycemia is the critical limiting factor in the glycemic management of diabetes in both the short and long term (1).

Clinicians have recognized the problem of iatrogenic hypoglycemia since the first use of insulin in 1922 (2). The problem was underscored 70 years later by the finding that intensive glycemic therapy both decreased the frequency of long-term complications and increased the frequency of hypoglycemia in the Diabetes Control and Complications Trial (DCCT) (3,4). Despite steady improvements in the glycemic management of diabetes, and perhaps because of the impetus for glycemic control that resulted from the DCCT (3,4) and the U.K. Prospective Diabetes Study (5,6), recent population-based data indicate that hypoglycemia continues to be a major problem for people with both type 1 and type 2 diabetes (7–9).

The ultimate goal of the glycemic management of diabetes is a lifetime of euglycemia without hypoglycemia. That will undoubtedly require glucose-regulated insulin replacement or secretion (10). Pending that, the goal of new drugs, devices, or management strategies to be used for the glycemic management

of diabetes is to both improve glycemic control and reduce the frequency and severity of hypoglycemia. How should new drugs, devices, or strategies be evaluated and reported from the perspective of hypoglycemia?

The American Diabetes Association assembled a Workgroup on Hypoglycemia in June of 2004 to discuss that issue and, in part, to advise the U.S. Food and Drug Administration as to how hypoglycemia should be used as an end point in studies of new treatments for diabetes. After reviewing the background of hypoglycemia in diabetes, the Workgroup discussed three questions: 1) How should hypoglycemia be defined? 2) How should hypoglycemia be reported? 3) What constitutes a meaningful reduction in hypoglycemia?

HYPOGLYCEMIA IN DIABETES

The topic of hypoglycemia in diabetes has been reviewed in detail recently (1,11). The clinical syndrome is most convincingly documented by Whipple's triad (12): symptoms consistent with hypoglycemia, a low plasma glucose concentration, and relief of those symptoms when the plasma glucose concentration is raised. In people with diabetes, hypoglycemia has been classified as "asymptomatic" or "biochemical," which is particularly common, and "symptomatic" or "severe," which requires the assistance of another individual. Symptoms of hypoglycemia may be idiosyncratic, but individuals often learn to recognize their unique symptoms. Neurogenic (autonomic) symptoms include, but are not

limited to, palpitations, tremor, hunger, and sweating. Neuroglycopenic symptoms often include behavioral changes, difficulty thinking, and/or frank confusion, but neuroglycopenic manifestations can include seizure, coma, and even death.

In people with diabetes, hypoglycemia is the result of the interplay of relative or absolute insulin excess and compromised physiological defenses against falling plasma glucose concentrations (1,11). Insulin excess from time to time is the result of the pharmacokinetic imperfections of all insulin preparations and insulin secretagogues used to treat diabetes in the context of an array of factors such as food intake, exercise, drug (including alcohol) interactions, altered sensitivity to insulin, and insulin clearance. Compromised physiological defenses against falling plasma glucose concentrations are the result of the pathophysiology of glucose counterregulation—the mechanisms that normally prevent or rapidly correct hypoglycemia—at least in type 1 and advanced type 2 diabetes. That pathophysiology includes impairment of all three key defenses against falling plasma glucose levels in the endogenous insulin deficient state: 1) insulin levels do not decrease, 2) glucagon levels do not increase, and 3) the increase in epinephrine levels is typically attenuated (i.e., the glycemic threshold for epinephrine secretion is shifted to a lower plasma glucose concentration). In the setting of absent insulin and glucagon responses, the attenuated epinephrine response causes the syndrome of defective glucose counterregulation. The attenuated sympathoadrenal (sympathetic neural as well as adrenomedullary) response also causes the clinical syndrome of hypoglycemia unawareness, i.e., loss of the warning symptoms that previously allowed the patient to recognize developing hypoglycemia and take corrective action. While the absent insulin and glucagon responses are persistent defects, it is now recognized that the reduced sympatho-

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Abbreviations: DCCT, Diabetes Control and Complications Trial.

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adrenal response to a given level of hypoglycemia is a dynamic process typically induced by recent antecedent iatrogenic hypoglycemia (1,11). The concept of hypoglycemia-associated autonomic failure in type 1 diabetes (13) and advanced type 2 diabetes (14) posits that recent antecedent hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response in the setting of absent insulin and glucagon responses) and hypoglycemia unawareness (by reducing the sympathoadrenal and the resulting symptomatic responses) and thus a vicious cycle of recurrent hypoglycemia (1,11). That concept has been extended recently to include exercise- and sleep-related hypoglycemia-associated autonomic failure (11). Thus, hypoglycemia unawareness is reversible in most affected patients, and the reduced epinephrine component of defective glucose counterregulation is variably improved, by as little as 2–3 weeks of scrupulous avoidance of iatrogenic hypoglycemia (15–19). Importantly, antecedent plasma glucose levels as high as 70 mg/dl (3.9 mmol/l) cause reduced sympathoadrenal responses to subsequent hypoglycemia (20).

Iatrogenic hypoglycemia often has a profound impact on the lives of people with diabetes (as well as on their physiological defenses against subsequent hypoglycemia). The experience of an episode can range from unrecognized to extremely uncomfortable and disrupting. As a group, people with diabetes fear hypoglycemia more than they fear the long-term complications of diabetes. The degree of cognitive-motor dysfunction, particularly slowing of cognitive and motor processing speed, during an episode depends on the magnitude of hypoglycemia. The psychological reactions can be quite frightening and can extend beyond the patient to include family, friends, and coworkers. If neuroglycopenia occurs while the individual is performing a critical task, such as driving, the individual and others are placed at risk of injury and death. The rational fear of hypoglycemia can lead to worsening of metabolic control as well as tension with, and a restriction of personal freedoms and responsibilities by, anxious and overprotective loved ones, colleagues, or employers.

Risk factors for hypoglycemia (1,11) include: 1) endogenous insulin deficiency, which also predicts a deficient

glucagon response; 2) a history of hypoglycemia, hypoglycemia unawareness, or both; 3) aggressive glycemetic therapy per se as evidenced by lower glycemetic goals, lower HbA_{1c} levels, or both; 4) recent moderate or intensive exercise; 5) sleep; and 6) renal failure. However, a history of severe hypoglycemia and lower HbA_{1c} levels have limited ability to predict additional episodes. These two parameters accounted for ~9% of future episodes of severe hypoglycemia in the DCCT (4) and, when combined with a specific autonomic score, for 18% of future severe hypoglycemic episodes (21).

Mild hypoglycemic episodes frequently precede severe hypoglycemia (22). Indeed, >50% of hypoglycemia can be predicted based on risk analysis of self-monitored plasma glucose data over time (23). This reflects the fact, discussed earlier, that recent antecedent hypoglycemia, with prior plasma glucose concentrations as high as 70 mg/dl (3.9 mmol/l) (20), causes defective glucose counterregulation and hypoglycemia unawareness (1,11). Thus, episodes of hypoglycemia not only cause recurrent physical and psychological morbidity and risk of death in the short term but also preclude euglycemia in the long term. In addition, episodes lead to a vicious cycle of recurrent hypoglycemia.

QUESTIONS

A) How should hypoglycemia be defined?

The Workgroup first established a set of guiding principles regarding the ideal definition of hypoglycemia in individuals with diabetes. First, the optimal definition should be applicable to clinical decision-making by people with diabetes and their care providers as well as to studies of diabetes drugs, devices, or management strategies, although the standards for documenting and reporting hypoglycemia in studies need to be more stringent than those in the clinical setting. Second, the definition should be 1) free from reporting biases, 2) clinically important, 3) applicable to all persons with diabetes, 4) applicable to any time of day, 5) measurable by practical and widely available methods, and 6) reportable in a standardized fashion.

Given these parameters, the Workgroup's overarching definition of hypoglycemia includes all episodes of an

abnormally low plasma glucose concentration that expose the individual to potential harm. With regard to the latter issue, it is not only the nadir glucose concentration and the duration of hypoglycemia that may be inherently dangerous; frequent hypoglycemic events interfere with daily living and, even if asymptomatic, lead to defective glucose counterregulation and hypoglycemia unawareness (1,11,13,14,20). Since these episodes increase the risk of subsequent hypoglycemia substantially, all hypoglycemic events can harm the individual with diabetes in the short or long term.

In addition to glucose counterregulatory systems that are triggered at an (arterialized venous) plasma glucose concentration of 65–70 mg/dl (3.6–3.9 mmol/l) in nondiabetic people (24–26), warning symptoms of hypoglycemia are critical to permit interventions that also restore the plasma glucose concentration toward normal. Thus, symptoms of a low plasma glucose, it can be argued, may be included in a definition of hypoglycemia. It is acknowledged that symptoms are idiosyncratic and nonspecific and may either not be recognized as such or be absent. Alternatively, it could be argued that hypoglycemia—literally low blood glucose—is by definition diagnosed by a low plasma glucose value. Thus, the question arises as to whether symptoms associated with hypoglycemia should ever replace a glucose value. Although it is appreciated that people with diabetes often know when they are hypoglycemic, there is also the very gray area that occurs when comorbid conditions or therapies produce symptoms similar to those that occur during hypoglycemia (e.g., palpitations, tremor, hunger, or sweating) or in patients with hypoglycemia unawareness. Clearly, it is important for patients to measure their glucose levels when they think they are hypoglycemic. The reality, however, is that a plasma glucose level is not always obtained.

Finally, the question arises as to how a glucose level used to define hypoglycemia should be measured. Although a precise laboratory-based plasma glucose measurement would be ideal, monitor-based estimates (or those with a validated glucose sensor) are the only practical method. Albeit a function of mean glycemia and therefore a useful index of overall glycemetic control and generally inversely related to the frequency of hypoglycemia, the HbA_{1c} level is not an alternative to plasma glucose values. Given that they

likely have periods of hyperglycemia, patients with near-normal HbA_{1c} levels likely have periods of hypoglycemia (e.g., during the night) whether they are detected or not.

The Workgroup definition describes a classification of hypoglycemic events based on the above considerations. A hypoglycemic episode could be:

1) Severe hypoglycemia. An event requiring assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

2) Documented symptomatic hypoglycemia. An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/l).

3) Asymptomatic hypoglycemia. An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤ 70 mg/dl (3.9 mmol/l). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65–70 mg/dl (3.6–3.9 mmol/l) (24–26) and since antecedent plasma glucose concentrations of ≤ 70 mg/dl (3.9 mmol/l) reduce sympathoadrenal responses to subsequent hypoglycemia (1,11,20), this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.

4) Probable symptomatic hypoglycemia. An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dl [3.9 mmol/l]). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as “probable” hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies

that are aimed at evaluating therapy, but they should be reported.

5) Relative hypoglycemia. An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration >70 mg/dl (3.9 mmol/l). This category reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels >70 mg/dl (3.9 mmol/l) as plasma glucose concentrations decline toward that level (27,28). Though causing distress and interfering with the patient’s sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and therefore may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

B) How should hypoglycemia be reported?

At a minimum, hypoglycemic events should be reported in each of the first three categories: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia. Thus, since severe hypoglycemia is infrequent, the vast majority of reported episodes will require a corresponding plasma glucose concentration <70 mg/dl (3.9 mmol/l), with (documented symptomatic hypoglycemia) or without (asymptomatic hypoglycemia) symptoms. Such relatively stringent criteria are appropriate for studies of new drugs, devices, or management strategies. Nonetheless, their use alone will underestimate the frequency of symptomatic episodes attributed to hypoglycemia. Therefore, it would be useful to also report episodes of probable symptomatic and relative hypoglycemia, even though these are not used as statistical outcome variables.

Currently there is no standardized convention for reporting the frequency of hypoglycemia in clinical studies. The Workgroup recommends that both the proportion (percentage) of patients affected and the event rates (e.g., episodes per patient-year or 100 patient-years) for each of the categories of hypoglycemic events be reported. These provide complementary information.

At least in type 1 diabetes, hypoglycemia occurs most frequently during sleep

(3,4). Episodes of nocturnal hypoglycemia range from asymptomatic to severe and are potentially fatal if untreated. In addition, even asymptomatic nocturnal hypoglycemia impairs defenses against subsequent hypoglycemia (29,30), i.e., it causes defective glucose counterregulation and hypoglycemia unawareness (1,11). Therefore, it is appropriate to separate hypoglycemic events into nocturnal and daytime episodes.

Finally, if patients at high risk for hypoglycemia are excluded from clinical studies, that exclusion should be made clear. Similarly, it should be made clear if patients at low risk are excluded. Obviously, the exclusion/inclusion criteria can affect the frequency of hypoglycemic events.

C) What constitutes a meaningful reduction in hypoglycemia?

Clearly, clinical approaches that reduce the severity of hypoglycemia, as well as those that reduce the frequency of hypoglycemia, would be worthwhile. The Workgroup concluded that any significant reduction in severe hypoglycemia (that requiring the assistance of another individual), even by as little as 10–20%, would be advantageous. It was the consensus of the Workgroup that a significant reduction in the frequency of documented hypoglycemia (plasma glucose <70 mg/dl [3.9 mmol/l]), with or without symptoms, of $\geq 30\%$ by a new drug, device, or management strategy would represent a clinically important improvement over existing therapies. That could be a $\geq 30\%$ reduction in the proportion of patients affected by hypoglycemia, the hypoglycemia event rates, or both. (Again, both the proportion of patients affected and the event rates should be reported.) The reduction in hypoglycemia could be over any clinically relevant period of time; if limited to a segment of the day, e.g., during the night, it should not be offset by an increase in the frequency of hypoglycemia in the remainder of the day. Finally, a clinically important reduction in hypoglycemia should not be accompanied by an increase in mean glycemia (e.g., HbA_{1c}). Indeed, as mentioned earlier, the goal is to reduce both hypoglycemia and glycemia.

Rates of hypoglycemia can vary within a given clinical study. The frequency of hypoglycemia could increase sharply early in a study with intensifica-

tion of treatment only to decrease to a lower steady state when a plateau of stable glycemic control is achieved. This initial phase of increased hypoglycemia can be variable and depends on factors such as the pharmacokinetics and pharmacodynamics of a new drug; the investigator and patient learning curve with a new drug, device, or strategy; and the rapidity of intensification of glycemic control. On the other hand, since the frequency of hypoglycemia is linked to glycemic control, a study that improves glucose levels slowly may produce a pattern of increasing rates of hypoglycemia over months. A third scenario is an experimental design that tests a chronic intervention over years.

Therefore, the experimental question is a key factor driving the assessment of the frequency of hypoglycemia. The sample size is, of course, another key variable. Thus, the metrics that should be considered in designing a study aimed at determining the frequency of hypoglycemia include: 1) the time required to achieve the glycemic target, 2) the duration of stable glycemic control, 3) the target level of glycemic control, and 4) the number of participants.

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APPENDIX

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