Hypoglycemia and Diabetes: A Report of a Workgroup of the American Diabetes Association and The Endocrine Society

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OBJECTIVE—To review the evidence about the impact of hypoglycemia on patients with diabetes that has become available since the past reviews of this subject by the American Diabetes Association and The Endocrine Society and to provide guidance about how this new information should be incorporated into clinical practice.

PARTICIPANTS—Five members of the American Diabetes Association and five members of The Endocrine Society with expertise in different aspects of hypoglycemia were invited by the Chair, who is a member of both, to participate in a planning conference call and a 2-day meeting that was also attended by staff from both organizations. Subsequent communications took place via e-mail and phone calls. The writing group consisted of those invitees who participated in the writing of the manuscript. The workgroup meeting was supported by educational grants to the American Diabetes Association from Lilly USA, LLC and Novo Nordisk and sponsorship to the American Diabetes Association from Sanofi. The sponsors had no input into the development of or content of the report.

EVIDENCE—The writing group considered data from recent clinical trials and other studies to update the prior workgroup report. Unpublished data were not used. Expert opinion was used to develop some conclusions.

CONSENSUS PROCESS—Consensus was achieved by group discussion during conference calls and face-to-face meetings, as well as by iterative revisions of the written document. The document was reviewed and approved by the American Diabetes Association's Professional Practice Committee in October 2012 and approved by the Executive Committee of the Board of Directors in November 2012 and was reviewed and approved by The Endocrine Society's Clinical Affairs Core Committee in October 2012 and by Council in November 2012.

CONCLUSIONS—The workgroup reconfirmed the previous definitions of hypoglycemia in diabetes, reviewed the implications of hypoglycemia on both short- and long-term outcomes, considered the implications of hypoglycemia on treatment outcomes, presented strategies to prevent hypoglycemia, and identified knowledge gaps that should be addressed by future research. In addition, tools for patients to report hypoglycemia at each visit and for clinicians to document counseling are provided.

In 2005, the American Diabetes Association Workgroup on Hypoglycemia released a report entitled "Defining and Reporting Hypoglycemia in Diabetes" (1). In that report, recommendations were primarily made to advise the U.S. Food and Drug Administration (FDA) on how hypoglycemia should be used as an end point in studies of new treatments for diabetes. In 2009, The Endocrine Society released a clinical practice guideline entitled "Evaluation and Management of Adult Hypoglycemic Disorders," which summarized how clinicians should manage hypoglycemia in patients with diabetes (2). Since then, new evidence has become available that links hypoglycemia with adverse outcomes in older patients with type 2 diabetes (3–6) and in children with type 1 diabetes (7,8). To provide guidance about how this new information should be incorporated into clinical practice, the American Diabetes Association and The Endocrine Society assembled a new Workgroup on Hypoglycemia in April 2012 to address the following questions:

1. How should hypoglycemia in diabetes be defined and reported?
2. What are the implications of hypoglycemia on both short- and long-term outcomes in people with diabetes?
3. What are the implications of hypoglycemia on treatment targets for patients with diabetes?

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4. What strategies are known to prevent hypoglycemia, and what are the clinical recommendations for those at risk for hypoglycemia?
5. What are the current knowledge gaps in our understanding of hypoglycemia, and what research is necessary to fill these gaps?

How should hypoglycemia in diabetes be defined and reported?

—Hypoglycemia puts patients at risk for injury and death. Consequently the workgroup defines iatrogenic hypoglycemia in patients with diabetes as all episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm. A single threshold value for plasma glucose concentration that defines hypoglycemia in diabetes cannot be assigned because glycemic thresholds for symptoms of hypoglycemia (among other responses) shift to lower plasma glucose concentrations after recent antecedent hypoglycemia (9–12) and to higher plasma glucose concentrations in patients with poorly controlled diabetes and infrequent hypoglycemia (13).

Nonetheless, an alert value can be defined that draws the attention of both patients and caregivers to the potential harm associated with hypoglycemia. The workgroup (1) suggests that patients at risk for hypoglycemia (i.e., those treated with a sulfonylurea, glinide, or insulin) should be alert to the possibility of developing hypoglycemia at a self-monitored plasma glucose—or continuous glucose monitoring subcutaneous glucose—concentration of ≤70 mg/dL (≤3.9 mmol/L). This alert value is data driven and pragmatic (14). Given the limited accuracy of the monitoring devices, it approximates the lower limit of the normal postabsorptive plasma glucose concentration (15), the glycemic thresholds for activation of glucose counterregulatory systems in nondiabetic individuals (15), and the upper limit of plasma glucose level reported to reduce counterregulatory responses to subsequent hypoglycemia (11). Because it is higher than the glycemic threshold for symptoms in both nondiabetic individuals and those with well-controlled diabetes (9,13,14), it generally allows time to prevent a clinical hypoglycemic episode and provides some margin for the limited accuracy of monitoring devices at low-glucose levels. People with diabetes need not always self-treat at an estimated glucose concentration of ≤70 mg/dL (≤3.9 mmol/L). Options other than carbohydrate ingestion include repeating the test in the short term, changing behavior (e.g., avoiding driving or elective exercise until the glucose level is higher), and adjusting the treatment regimen. Although this alert value has been debated (9,13,14), a plasma concentration of ≤70 mg/dL (≤3.9 mmol/L) can be used as a cut-off value in the classification of hypoglycemia in diabetes.

Consistent with past recommendations (1), the workgroup suggests the following classification of hypoglycemia in diabetes:

1) Severe hypoglycemia. Severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

2) Documented symptomatic hypoglycemia. Documented symptomatic hypoglycemia is 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. Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L).

4) Probable symptomatic hypoglycemia. Probable symptomatic hypoglycemia is an event during which symptoms typical 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).

5) Pseudo-hypoglycemia. Pseudohypoglycemia is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia with a measured plasma glucose concentration >70 mg/dL (>3.9 mmol/L) but approaching that level.

The challenge of measuring glucose accurately

Currently, two technologies are available to measure glucose in outpatients: capillary measurement with point-of-care (POC) glucose meters (self-monitored blood glucose [SMBG]) and interstitial measurement with continuous glucose monitors (CGMs), both retrospective and real time. The International Organization for Standardization (ISO) and FDA standards require that POC meters' analytical accuracy be within 20% of the actual value in 95% of samples with glucose levels ≥75 mg/dL and ±15 mg/dL for samples with glucose <75 mg/dL. Despite this relatively large permissible variation, Freckmann et al. (16) found that only 15 of 27 meters on the market in Europe several years ago met the current analytical standards of ±15 mg/dL in the hypoglycemia range, 2 of 27 met ±10 mg/dL, and none were capable of measuring ±5 mg/dL.

The need for accurate meters in the <75 mg/dL range is essential in insulin-treated patients, whether they are outpatients or inpatients, but it is less important in those outpatients who are on medications that rarely cause hypoglycemia. In critical care units, where the accuracy of POC meters is particularly crucial, their performance may be compromised by medications (vasopressors, acetaminophen), treatments (oxygen), and clinical states (hypotension, anemia) (17). Karon et al. (18) translated these measurement errors into potential insulin-dosing errors using simulation modeling and found that if there were a total measurement error of 20%, 1- and 2-step errors in insulin dose would occur 45% and 6% of the time, respectively, in a tight glycemic control protocol. Such imprecision may affect the safe implementation of insulin infusion protocols in critical care units and may account in part for the high hypoglycemia rates in most trials of inpatient intensive glycemic control.

Retrospective and real-time CGMs represent an evolving technology that has made considerable progress in overall (point + rate) accuracy. However, the accuracy of CGMs in the hypoglycemic range is poor as demonstrated by error grid analysis (19,20). With existing real-time CGMs, accuracy can be achieved in only 60–73% of samples in the range of 40–80 mg/dL (21,22). Because the accuracy of CGMs, like POC meters, is negatively affected by multiple factors in hospitalized patients and they are calibrated with POC meters affected by those same factors, CGMs are not recommended for glycemic management in hospitalized patients at this time (17).

What are the implications of hypoglycemia on both short- and long-term outcomes in people with diabetes?

—Iatrogenic hypoglycemia is more frequent in patients with profound endogenous insulin deficiency—type

1 diabetes and advanced type 2 diabetes—and its incidence increases with the duration of diabetes (23). It is caused by treatment with a sulfonylurea, glinide, or insulin and occurs about two to three times more frequently in type 1 diabetes than in type 2 diabetes (23,24). Event rates for severe hypoglycemia for patients with type 1 diabetes range from 115 (24) to 320 (23) per 100 patient-years. Severe hypoglycemia in patients with type 2 diabetes has been shown to occur at rates of 35 (24) to 70 (23) per 100 patient-years. However, because type 2 diabetes is much more prevalent than type 1 diabetes, most episodes of hypoglycemia, including severe hypoglycemia, occur in people with type 2 diabetes (25).

There is no doubt that hypoglycemia can be fatal (26). In addition to case reports of hypoglycemic deaths in patients with type 1 and type 2 diabetes, four recent reports of mortality rates in series of patients indicate that 4% (27), 6% (28), 7% (29), and 10% (30) of deaths of patients with type 1 diabetes were caused by hypoglycemia. A temporal relationship between extremely low subcutaneous glucose concentrations and death in a patient with type 1 diabetes who was wearing a CGM device and was found dead in bed has been reported (31). Although profound and prolonged hypoglycemia can cause brain death, most episodes of fatal hypoglycemia are probably the result of other mechanisms, such as ventricular arrhythmias (26). In this section, we will consider the effects of hypoglycemia on the development of hypoglycemia unawareness and how iatrogenic hypoglycemia may affect outcomes in specific patient groups.

Hypoglycemia unawareness and hypoglycemia-associated autonomic failure

Acute hypoglycemia in patients with diabetes can lead to confusion, loss of consciousness, seizures, and even death, but how a particular patient responds to a drop in glucose appears to depend on how frequently that patient experiences hypoglycemia. Recurrent hypoglycemia has been shown to reduce the glucose level that precipitates the counterregulatory response necessary to restore euglycemia during a subsequent episode of hypoglycemia (10–12). As a result, patients with frequent hypoglycemia do not experience the symptoms from the adrenergic response to a fall in glucose until the blood glucose reaches lower and lower levels. For some individuals, the level that triggers the response is below the glucose level associated with neuroglycopenia. The first sign of hypoglycemia in these patients is confusion, and they often must rely on the assistance of others to recognize and treat low blood glucose. Such individuals are said to have developed hypoglycemia unawareness. Defective glucose counterregulation (the result of loss of a decrease in insulin production and an increase in glucagon release along with an attenuated increase in epinephrine) and hypoglycemia unawareness (the result of an attenuated increase in sympathoadrenal activity) are the components of hypoglycemia-associated autonomic failure (HAAF) in patients with diabetes. HAAF is a form of functional sympathoadrenal failure that is most often caused by recent antecedent iatrogenic hypoglycemia (25) and is at least partly reversible by scrupulous avoidance of hypoglycemia (32–34). Indeed, HAAF has been shown to be maintained by recurrent iatrogenic hypoglycemia (33,34). The development of HAAF is associated with a 25-fold (35) or greater (36) increased risk of severe hypoglycemia during intensive glycemic therapy. It is important to distinguish HAAF from classical autonomic neuropathy, which may occur as one form of diabetic neuropathy. Impaired sympathoadrenal activation is generally confined to the response to hypoglycemia, and autonomic activities in organs such as the heart, gastrointestinal tract, and bladder appear to be unaffected.

Clinically, HAAF can be viewed as both adaptive and maladaptive. On the one hand, patients with hypoglycemia unawareness and type 1 diabetes appear to perform better on tests of cognitive function during hypoglycemia than do patients who are able to detect hypoglycemia normally (37). In addition, the time necessary for full cognitive recovery after restoration of euglycemia appears to be faster in patients who have hypoglycemia unawareness than in patients with normal detection of hypoglycemia (37). The HAAF habituation of the sympathoadrenal response to recurrent hypoglycemic stress in humans (38) may be analogous to the phenomenon of habituation of the hypothalamic-pituitary-adrenocortical response to recurrent restraint stress in rats (39). Rats subjected to recurrent moderate hypoglycemia had less brain cell death (40) and less mortality (41) during or following marked hypoglycemia than those not subjected to recurrent hypoglycemia.

On the other hand, HAAF is clearly maladaptive since defective glucose counterregulation and hypoglycemia unawareness substantially increase the risk of severe hypoglycemia with its morbidity and potential mortality (26). A particularly low plasma glucose concentration might trigger a robust, potentially fatal sympathoadrenal discharge. Life-threatening episodes of hypoglycemia need not be frequent to be devastating.

Impact of hypoglycemia on children with diabetes

Hypoglycemia is a common problem in children with type 1 diabetes because of the challenges presented by insulin dosing, variable eating patterns, erratic activity, and the limited ability of small children to detect hypoglycemia. The infant, young child, and even the adolescent typically exhibit unpredictable feeding—not eating all the anticipated food at a meal and snacking unpredictably between meals—and have prolonged periods of fasting overnight that increase the risk of hypoglycemia. Selecting the correct prandial dose of insulin is therefore often difficult. Very low insulin requirements for basal and mealtime dosing in the infant and young child frequently require use of miniscule basal rates in pump therapy and one-half unit dosing increments with injections. Management rarely requires the use of diluted insulin, e.g., 10 units per mL. Infants and toddlers may not recognize the symptoms of hypoglycemia and lack the ability to effectively communicate their distress. Caregivers must be particularly aware that changes in behavior such as a loss of temper may be a sign of hypoglycemia.

Puberty is associated with insulin resistance, while at the same time the normal developmental stages of adolescence may lead to inattention to diabetes and increased risk for hypoglycemia. As children grow, they often have widely fluctuating levels of activity during the day, which puts them at risk for hypoglycemia. Minimizing the impact of hypoglycemia on children with diabetes requires the education and engagement of parents, patients, and other caregivers in the management of the disease (42,43).

The youngest patients are most vulnerable to the adverse consequences of hypoglycemia. Ongoing maturation of the central nervous system puts these children at greater risk for cognitive deficits as a consequence of hypoglycemia (44). Recent studies have examined the

impact of hypoglycemia on cognitive function and cerebral structure in children and found that those who experience this complication before the age of 5 years seem to be more affected than those who do not have hypoglycemia until later (7). The long-term impact of hypoglycemia on cognition before the age of 5 years is unknown.

Impact of hypoglycemia on adults with type 1 diabetes

Landmark data on the impact of hypoglycemia on adults with type 1 diabetes come from the Diabetes Control and Complications Trial (DCCT) and its follow-up study, where cognition has been systematically measured over time. In this cohort, performance on a comprehensive battery of neurocognitive tests at 18 years of follow-up was the same in participants with and without a history of severe hypoglycemia (28). Despite such reassuring findings, recent investigation with advanced imaging techniques has demonstrated that adults with type 1 diabetes appear to call upon a greater volume of the brain to perform a working memory task during hypoglycemia (45). These findings suggest that adults with type 1 diabetes must recruit more regions to preserve cognitive function during hypoglycemia than adults without the disease. More work will be necessary to understand the significance of these observations on the long-term cognitive ability of adults with type 1 diabetes.

Impact of hypoglycemia on patients with type 2 diabetes

There is growing evidence that patients with type 2 diabetes might be particularly vulnerable to adverse events associated with hypoglycemia. Over the last decade, three large trials examined the effect of glucose lowering on cardiovascular events in patients with type 2 diabetes: ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial). Between them, a total of 24,000 patients with high cardiovascular risk were randomly assigned to either intensive glycemic control or standard therapy (3–5). In each, subjects who were randomly assigned to the intensive arm experienced more episodes of hypoglycemia than did those who were randomly assigned to the standard treatment arm. In the ACCORD trial, subjects who were randomly assigned to the intensive arm also experienced a 20% increase in mortality, and the glycemic control study was stopped early due to this finding. A relationship between mortality and randomization to intensive glucose control was not observed in ADVANCE or VADT, although VADT was underpowered to explore this relationship. A number of explanations have been offered to explain the findings of ACCORD, including chance, greater weight gain, and specific medication effects, but perhaps the most convincing candidate was hypoglycemia, which was threefold higher in the intensive arm of ACCORD (4).

In the opinion of the blinded adjudication committee assigned to investigate mortality in ACCORD, hypoglycemia was judged to have a definite role in only one death, a probable role in three deaths, and a possible role in 38 deaths (46), which represents a role in less than 10% of the deaths recorded in the study population while the glycemic intervention was active. The investigators thus suggest that hypoglycemia at the time of death was probably not responsible for the increased mortality rate in the intensive arm of ACCORD. Since glycemia was not measured at the time of death in any of the ACCORD subjects, we may never know. However, the potential lethal mechanisms that might be provoked by hypoglycemia could cause mortality downstream of the hypoglycemic event, increasing the difficulty in establishing cause and effect.

All three trials clearly demonstrated that an episode of severe hypoglycemia was associated with an increased risk of subsequent mortality. In ACCORD, those who had one or more severe hypoglycemic episodes had higher rates of death than those without such episodes across both study arms (hazard ratio 1.41 [95% CI 1.03–1.93]) (46). One-third of all deaths were due to cardiovascular disease, and hypoglycemia was associated with higher cardiovascular mortality. In VADT, a recent severe hypoglycemic event was the strongest independent predictor of death at 90 days (3). In ADVANCE, where rates of hypoglycemia were low, a similar pattern was found (47). Of course, in post hoc analyses a causal relationship cannot be established with certainty. It is possible that the association between hypoglycemia and death may be merely an indicator for vulnerability for death from any cause.

The relationship between hypoglycemia and subsequent cognitive function in patients with type 2 diabetes has also been investigated. In a large population study, hypoglycemic episodes that required hospitalization or a visit to the emergency department between 1980 and 2002 were associated with approximately double the risk of incident dementia after 2003 (6). However, since the study population did not undergo detailed tests of cognitive function prior to 2003, it is possible that those with incident dementia actually had mild cognitive dysfunction prior to experiencing the episode(s) of severe hypoglycemia. The possibility that mild cognitive dysfunction might increase the risk of experiencing severe hypoglycemia has been supported by analyses from the ACCORD study (48). In the ACCORD MIND (Memory IN Diabetes) study, in which cognitive function was assessed longitudinally, no difference was noted in the rate at which cognitive performance declined over time in subjects randomly assigned to the intensive versus the standard glucose arms despite the fact that they experienced three times as much hypoglycemia (49). Future investigation will need to address this question because the existing data are somewhat contradictory.

Impact of hypoglycemia on the elderly

Patients in the older age-groups are especially vulnerable to hypoglycemia. Epidemiological studies show that hypoglycemia is the most frequent metabolic complication experienced by older adults in the U.S. (50). Although severe hypoglycemia is common in older individuals with both type 1 and type 2 diabetes, patients with type 2 diabetes tend to have longer hospital stays and greater medical costs. The most significant predictors of this condition are advanced age, recent hospitalization, and polypharmacy, as shown in a study of Tennessee Medicare patients (51). Age-related declines in renal function and hepatic enzyme activity may interfere with the metabolism of sulfonylureas and insulin, thereby potentiating their hypoglycemic effects. The vulnerability of the elderly to severe hypoglycemia may be partially related to a progressive age-related decrease in β-adrenergic receptor function (52). Age-related impairment in counterregulatory hormone responses has been described in elderly patients with diabetes, especially with respect to glucagon and growth hormone (53). Symptoms of neuroglycopenia are more prevalent (54). With the prolonged duration of type 2

diabetes as is often seen in the elderly patient, the glucagon response to hypoglycemia is virtually absent (55). The intensification of glycemic control in the elderly patient is associated with an increased reduction in the plasma glucose thresholds for epinephrine release and for the appearance of hypoglycemia (56). As a result, changes in the level of glycemic control have a marked impact on the risk of developing hypoglycemia in the elderly.

Older adults with diabetes have a disproportionately high number of clinical complications and comorbidities, all of which can be exacerbated by and sometimes contribute to episodes of hypoglycemia. Older adults with diabetes are at much higher risk for the geriatric syndrome, which includes falls, incontinence, frailty, cognitive impairment, and depressive symptoms (57). The cognitive and executive dysfunction associated with the geriatric syndrome interferes with the patient's ability to perform self-care activities appropriately and follow the treatment regimen (58).

To minimize the risk of hypoglycemia in the elderly, careful education regarding the symptoms and treatment of hypoglycemia, with regular reinforcement, is extremely important because of the recognized gaps in the knowledge base of these individuals (59). In addition, it is important to assess the elderly for functional status as part of the overall clinical assessment in order to properly apply individualized glycemic control goals. Arbitrary short-acting insulin sliding scales, which are used much too often in long-term care facilities (60), should be avoided, and glyburide should be discontinued in favor of shorter-acting insulin secretagogues or medications that do not cause hypoglycemia. The recently published 2012 Beers list of prohibited medications in long-term care facilities specifically lists insulin sliding scales and glyburide as treatment modalities that should be avoided (61). Complex regimens requiring multiple decision points should be simplified, especially for patients with decreased functional status. In addition, caregivers and staff in long-term care facilities need to be educated on the causes and risks of hypoglycemia and the proper surveillance and treatment of this condition.

Impact of hypoglycemia on hospitalized patients

Persons with diabetes are three times more likely to be hospitalized than those without diabetes, and approximately 25% of hospitalized patients (including people without a history of diabetes) have hyperglycemia (62–65). Inpatient hyperglycemia has been associated with prolonged hospital length of stay and with numerous adverse outcomes including mortality (64,66–68). The understandable zeal to minimize the adverse consequences of inpatient hyperglycemia, together with the demonstration that intensive glycemic control improved outcomes in surgical intensive care unit (ICU) patients (69), led to widespread adoption of aggressive glucose management among ICU patients. However, subsequent studies showed that such aggressive lowering of glycemia in the ICU is not uniformly beneficial, markedly increases the risk of severe hypoglycemia, and may be associated with increased mortality (70–74).

The true incidence and prevalence of hypoglycemia among hospitalized patients with diabetes are not known precisely. In a retrospective study of 31,970 patients admitted to the general wards of an academic medical center in 2007, a total of 3,349 patients (10.5%) had at least one episode of hypoglycemia (≤70 mg/dL) (75). In another review of 5,365 inpatients admitted to ICUs, 102 (1.9%) had at least one episode of severe hypoglycemia (<40 mg/dL) (76). The risk factors for inpatient hypoglycemia include older age, presence of comorbidities, diabetes, increasing number of antidiabetic agents, tight glycemic control, septic shock, renal insufficiency, mechanical ventilation, and severity of illness (75,76). With regard to impact, a retrospective analysis of 4,368 admissions involving 2,582 diabetic patients admitted to the general ward indicated that severe hypoglycemia (≤50 mg/dL) was associated with increased length of stay and greater odds of inpatient death and death within 1 year of hospital discharge (77).

Impact of hypoglycemia during pregnancy

Maintaining blood glucose control in pregnancy as close to that of healthy pregnant women is important in minimizing the negative effects on the mother and the fetus (78). This is true for women with pregestational type 1 or type 2 diabetes, as well for those with gestational diabetes mellitus. Normal blood glucose levels during pregnancy are 20% lower than in nonpregnant women (79), making the definition and detection of hypoglycemia more challenging. For women with type 1 diabetes, severe hypoglycemia occurs 3–5 times more frequently in the first trimester and at a lower rate in the third trimester when compared with the incidence in the year preceding the pregnancy (80). Risk factors for severe hypoglycemia in pregnancy include a history of severe hypoglycemia in the preceding year, impaired hypoglycemia awareness, long duration of diabetes, low HbA_{1c} in early pregnancy, fluctuating plasma glucose levels, and excessive use of supplementary insulin between meals. Surprisingly, nausea and vomiting during pregnancy did not appear to add significant risk. When pregnant and nonpregnant women are compared with CGM, mild hypoglycemia (defined by the authors as blood glucose <60 mg/dL) is more common in all pregnant women, but equally so regardless of whether or not they have diabetes, either pregestational or gestational (81). Hypoglycemia is generally without risk for the fetus as long as the mother avoids injury during the episode. For women with preexisting diabetes, insulin requirements rise throughout the pregnancy and then drop precipitously at the time of delivery of the placenta, requiring an abrupt reduction in insulin dosing to avoid postdelivery hypoglycemia. Breastfeeding may also be a risk factor for hypoglycemia in women with insulin-treated diabetes (82).

Impact of hypoglycemia on quality of life and activities of daily living

Hypoglycemia and the fear of hypoglycemia have a significant impact on quality-of-life measures in patients with both type 1 and type 2 diabetes (83). Nocturnal hypoglycemia in particular may impact one's sense of well-being on the following day because of its impact on sleep quantity and quality (84). Patients with recurrent hypoglycemia have been found to have chronic mood disorders including depression and anxiety (85,86), although it is hard to establish cause and effect between hypoglycemia and mood changes. Interpersonal relationships may suffer as a result of hypoglycemia in patients with diabetes. In-depth interviews of a small group of otherwise healthy young adults with type 1 diabetes revealed the presence of interpersonal conflict including fears of dependency and loss of control. These adults also reported difficulty talking about issues related to hypoglycemia with significant others (87). This difficulty may carry over to their work life, where hypoglycemia has been linked to reduced productivity (88). Hypoglycemia

also impairs one's ability to drive a car (89–91), and many jurisdictions require documentation that severe hypoglycemia is not occurring before persons with diabetes are permitted to have a license to operate a motor vehicle (92). However, impaired awareness of hypoglycemia has not consistently been associated with an increased risk of car collisions (92–95).

What are the implications of hypoglycemia on treatment targets for patients with diabetes?—The glycemic target established for any given patient should depend on the patient's age, life expectancy, comorbidities, preferences, and an assessment of how hypoglycemia might impact his or her life. This patient-centered approach requires that clinicians spend time developing an individualized treatment plan with each patient. For very young children, the risks of severe hypoglycemia on brain development may require a strategy that attempts to avoid hypoglycemia at all costs. For healthy adults with diabetes, a reasonable glycemic goal might be the lowest HbA_{1c} that does not cause severe hypoglycemia, preserves awareness of hypoglycemia, and results in an acceptable number of documented episodes of symptomatic hypoglycemia. With current therapies, a strategy that completely avoids hypoglycemia may not be possible in patients with type 1 diabetes who strive to minimize their risks of developing the microvascular complications of the disease. However, glycemic goals might reasonably be relaxed in patients with long-standing type 1 diabetes and advanced complications or in those who are free of complications but have a limited life expectancy because of another disease process. In such patients, the glycemic goal could be to achieve glucose levels sufficiently low to prevent symptoms of hyperglycemia.

For patients with type 2 diabetes, the risk of hypoglycemia depends on the medications used (96). Early in the course of the disease, most patients are treated with lifestyle changes and metformin, neither of which causes hypoglycemia. Therefore, an HbA_{1c} of $<7\%$ is appropriate for many patients with recent-onset type 2 diabetes. As the disease progresses, it is likely that medications that increase the risk of hypoglycemia will be added. This, plus the presence of complications or comorbidities that limit life expectancy, means that glycemic goals may need to be less aggressive. While the benefits of achieving an HbA_{1c} of $<7\%$ may continue to be advocated for patients with type 2 diabetes at risk for microvascular complications and with sufficient life expectancy, less aggressive targets may be appropriate in those with known cardiovascular disease, extensive comorbidities, or limited life expectancy.

Older individuals with gait imbalance and frailty may experience a life-changing injury if they fall during a hypoglycemia episode, so avoiding hypoglycemia is paramount in such patients. Patients with cognitive dysfunction may have difficulty adhering to a complicated treatment strategy designed to achieve a low HbA_{1c} (48). Such patients will benefit from a simplification of the treatment strategy with a goal to prevent hypoglycemia as much as possible. Furthermore, the benefits of aggressive glycemic therapy in those affected are unclear.

What strategies are known to prevent hypoglycemia, and what are the clinical recommendations for those at risk for hypoglycemia?—Recurrent hypoglycemia increases the risk of severe hypoglycemia and the development of hypoglycemia unawareness and HAAF. Effective approaches known to decrease the risk of iatrogenic hypoglycemia include patient education, dietary and exercise modifications, medication adjustment, careful glucose monitoring by the patient, and conscientious surveillance by the clinician.

Patient education

There is limited research related to the influence of self-management education on the incidence or prevention of hypoglycemia. However, there is clear evidence that diabetes education improves patient outcomes (97–99). As part of the educational plan, the individual with diabetes and his or her domestic companions need to recognize the symptoms of hypoglycemia and be able to treat a hypoglycemic episode properly with oral carbohydrates or glucagon. Hypoglycemia, including its risk factors and remediation, should be discussed routinely with patients receiving treatment with insulin or sulfonylurea/glinide drugs, especially those with a history of recurrent hypoglycemia or impaired awareness of hypoglycemia. In addition, patients must understand how their medications work so they can minimize the risk of hypoglycemia. Care should be taken to educate patients on the typical pharmacokinetics of these medications. When evaluating a patient's report of hypoglycemia, it is important to adopt interviewing approaches that guide the patient to a correct identification of the precipitating factors of the episodes of hypoglycemia. Such a heuristic review of likely factors (skipped or inadequate meal, unusual exertion, alcohol ingestion, insulin dosage mishaps, etc.) in the period prior to the event can deepen the patient's appreciation of the behavioral factors that predispose to hypoglycemia.

There is convincing evidence that formal training programs that teach patients to replace insulin "physiologically" by giving background and mealtime/correction doses of insulin can reduce the risk of severe hypoglycemia. The Insulin Treatment and Training programs developed by Mühlhauser and Berger (100) have reported improved glycemic control comparable with DCCT while reducing the rates of severe hypoglycemia (101,102). These programs have been successfully delivered in other settings (103,104) with comparable reductions in hypoglycemic risk (105). Patients with frequent hypoglycemia may also benefit from enrollment in a blood glucose awareness training program. In such a program, patients and their relatives are trained to recognize subtle cues and early neuroglycopenic indicators of evolving hypoglycemia and respond to them before the occurrence of disabling hypoglycemia (106,107).

Dietary intervention

Patients with diabetes need to recognize which foods contain carbohydrates and understand how the carbohydrates in their diet affect blood glucose. To avoid hypoglycemia, patients on long-acting secretagogues and fixed insulin regimens must be encouraged to follow a predictable meal plan. Patients on more flexible insulin regimens must know that prandial insulin injections should be coupled to meal times. Dissociated meal and insulin injection patterns lead to wide fluctuations in plasma glucose levels. Patients on any hypoglycemia-inducing medication should also be instructed to carry carbohydrates with them at all times to treat hypoglycemia.

The best bedtime snack to prevent overnight hypoglycemia in patients with type 1 diabetes has been investigated

without clear consensus (108–112). These conflicting reports suggest that the administration of bedtime snacks may need to be individualized and be part of a comprehensive strategy (balanced diet, patient education, optimized drug regimens, and physical activity counseling) for the prevention of nocturnal hypoglycemia.

Exercise management

Physical activity increases glucose utilization, which increases the risk of hypoglycemia. The risk factors for exertional hypoglycemia include prolonged exercise duration, unaccustomed exercise intensity, and inadequate energy supply in relation to ambient insulinemia (113,114). Postexertional hypoglycemia can be prevented or minimized by careful glucose monitoring before and after exercise and taking appropriate preemptive actions. Preexercise snacks should be ingested if blood glucose values indicate falling glucose levels. Patients with diabetes should carry readily absorbable carbohydrates when embarking on exercise, including sporadic house or yard work. Because of the kinetics of rapid-acting and intermediate-acting insulin, it may be prudent to empirically adjust insulin doses on the days of planned exercise, especially in patients with well-controlled diabetes with a history of exercise-related hypoglycemia.

Medication adjustment

Hypoglycemic episodes that are not readily explained by conventional factors (skipped or irregular meals, unaccustomed exercise, alcohol ingestion, etc.) may be due to excessive doses of drugs used to treat diabetes. A thorough review of blood glucose patterns may suggest vulnerable periods of the day that mandate adjustments to the current antidiabetes regimen. Such adjustments may include substitution of rapid-acting insulin (lispro, aspart, glulisine) for regular insulin, or basal insulin glargine or detemir for NPH, to decrease the risk of hypoglycemia. Continuous subcutaneous insulin infusion offers great flexibility for adjusting the doses and administration pattern of insulin to counteract iatrogenic hypoglycemia (115). For patients with type 2 diabetes, sulfonylureas are the oral agents that pose the greatest risk for iatrogenic hypoglycemia and substitution with other classes of oral agents or even glucagon-like peptide 1 analogs should be considered in the event of troublesome hypoglycemia (96). Interestingly, successful transplantation of whole pancreata or isolated pancreatic islet cells in patients with type 1 diabetes (116–118) results in marked improvements in glycemic control and near abolition of iatrogenic hypoglycemia.

Patients who develop hypoglycemia unawareness do so because of frequent and recurrent hypoglycemia. To avoid such frequent hypoglycemia, adjustments in the treatment regimen that scrupulously avoid hypoglycemia are necessary (Table 1). In published studies, this has required frequent (almost daily) contact between clinician and patient, and adjustments to caloric intake and insulin regimen based on blood glucose values (10,119,120). With this approach, restoration of autonomic symptoms of hypoglycemia occurred within 2 weeks, and complete reversal of hypoglycemia unawareness was achieved by 3 months. In some but not all reports, the recovery of symptoms is accompanied by the improvement in epinephrine secretion (32,33,120,121). The return of hypoglycemic symptom awareness was associated with a modest increase (~0.5%) in HbA_{1c} values (33), but others have reported no loss of glycemic control (32,34).

Glucose monitoring

Glucose monitoring is essential in managing patients at risk for hypoglycemia. Patients treated with insulin, sulfonylureas, or glinides should check their blood glucose whenever they develop the symptoms of hypoglycemia in order to confirm that they must ingest carbohydrates to treat the symptoms and collect information that can be used by the clinician to adjust the therapeutic regimen to avoid future hypoglycemia. Patients on basal-bolus insulin therapy should check their blood glucose before each meal and figure this value into the calculation of the dose of rapid-acting insulin to take at that time. Such care in dosing will likely reduce the risk of hypoglycemia.

Recent technological developments have provided patients with new tools for glucose monitoring. Real-time CGM, by virtue of its ability to display the direction and rate of change, provides helpful information to the wearer leading to proactive measures to avoid hypoglycemia, e.g., when to think about having a

Table 1—*Approach to restore recognition of hypoglycemia in patients with HAAF*

Monitoring and goal setting
Encourage SMBG before meals, at bedtime, and during suggestive symptoms
Encourage SMBG between 2 A.M. and 5 A.M. at least three times weekly
Set targets for preprandial blood glucose levels at 100–150 mg/dL
Patient education
Educate patients on hypoglycemic symptoms and the role of recurrent hypoglycemia in the etiology of hypoglycemia unawareness
Reassure patients that hypoglycemia unawareness is reversible through avoidance of hypoglycemia
Train patients to recognize and respond promptly to early neuroglycopenic symptoms
Dietary intervention
Ensure adequate caloric intake
Recommend interprandial and bedtime snacks
Ensure access to readily absorbable carbohydrates at all times
Consider moderate amounts of xanthine beverages, if tolerated
Exercise counseling
Encourage SMBG before, during, and after exercise
Advise preexercise caloric intake if blood glucose is <140 mg/dL
Advise consumption of additional calories during and after exercise if blood glucose is <140 mg/dL
Medication adjustment
Adjust insulin regimen to achieve and maintain target glucose levels
Use rapid-acting insulin analogs (lispro, aspart, glulisine) to decrease the risk of interprandial hypoglycemia
Use basal insulin analogs (glargine, detemir) to decrease the risk of nocturnal hypoglycemia
Consider a continuous subcutaneous insulin infusion pump, as appropriate
Consider a CGM device

Adapted from reference 125.

snack or suspending insulin delivery on a pump. The CGM's audible and/or vibratory alarms may be particularly helpful in avoiding severe hypoglycemia at night and restoring hypoglycemic awareness. With the low-glucose alarms set at 108 mg/dL, 4 weeks of real-time CGM use restored the epinephrine response and improved adrenergic symptoms during a hyperinsulinemic hypoglycemic clamp in a small group of adolescents with type 1 diabetes and hypoglycemic unawareness (122).

The artificial pancreas, which couples a CGM to an insulin pump through sophisticated predictive algorithms, holds out the promise of completely eliminating hypoglycemia. Several internationally collaborative groups are working on various approaches to the artificial pancreas. The first step in this direction is the low-glucose suspend pump that is available in Europe and currently in clinical trials in the U.S. This device shuts off insulin delivery for up to 2 h once the interstitial glucose concentration reaches a preset threshold and reduces the duration of nocturnal hypoglycemia (123).

Table 2—*Hypoglycemia Patient Questionnaire*

Name _____
First Middle Last
Today's date _____

1. To what extent can you tell by your symptoms that your blood glucose is LOW?
____ Never ____ Rarely ____ Sometimes ____ Often ____ Always

2. In a typical week, how many times will your blood glucose go below 70 mg/dL?
_____ a week

3. When your blood glucose goes below 70 mg/dL, what is the usual reason for this?
_____

4. How many times have you had a severe hypoglycemic episode (where you needed someone's help and were unable to treat yourself)?
Since the last visit ____ times
In the last year ____ times

5. How many times have you had a moderate hypoglycemic episode (where you could not think clearly, properly control your body, had to stop what you were doing, but you were still able to treat yourself)?
Since the last visit ____ times
In the last year _____ times

6. How often do you carry a snack or glucose tablets (or gel) with you to treat low blood glucose? Check one of the following:
Never ___ Rarely ___ Sometimes___ Often___ Almost always___

7. How LOW does your blood glucose need to go before you think you should treat it?
Less than ____mg/dL

8. What and how much food or drink do you usually treat low blood glucose with?
_____

9. Do you check your blood glucose before driving? Check one of the following:
Yes, always___ Yes, sometimes ___ No___

10. How LOW does your blood glucose need to go before you think you should not drive?
____mg/dL

11. How many times have you had your blood glucose below 70 mg/dL while driving?
Since the last visit ____ times
In the last year _____ times

12. If you take insulin, do you have a glucagon emergency kit?
Yes___/ No ___

13. Does a spouse, relative, or other person close to you know how to administer glucagon?
Yes___/ No ___

Clinical surveillance

Clinicians and educators must assess the risk of hypoglycemia at every visit with patients treated with insulin and insulin secretagogues. An efficient way to begin this assessment might be to have the patient complete the questionnaire shown in Table 2 while in the waiting room. Review of the completed questionnaire will help the clinician learn how often the patient is experiencing symptomatic and asymptomatic hypoglycemia, ensure the patient is aware of how to appropriately treat hypoglycemia, and remind both parties of the risks associated with driving while hypoglycemic. To ensure that hypoglycemia has been adequately addressed during a visit, providers may want to use the Hypoglycemia Provider Checklist (Table 3).

A careful review of the glucose log collected by the patient should also be done at each visit. The date, approximate time, and circumstances surrounding recent episodes of hypoglycemia should be noted, together with information regarding the awareness of the warning symptoms of hypoglycemia. A reliable history of impaired autonomic responses (tremulousness, sweating, palpitations, and hunger) during hypoglycemia may be the most practical approach to making the diagnosis of hypoglycemia unawareness. If symptoms are absent or if frequent episodes of recurrent hypoglycemia occur within hours to days of each other, it is likely that the patient has HAAF. Other historical clues such as experiencing more than one episode of severe hypoglycemia that required the assistance of another over the preceding year or a family report that they are recognizing more frequent episodes of hypoglycemia may also provide clues that the patient has developed hypoglycemia unawareness. A self-reported history of impaired or absent perception of autonomic symptoms during hypoglycemia correlates strongly with laboratory confirmation of hypoglycemia unawareness (33,121,124,125).

Table 3—*Hypoglycemia Provider Checklist*

Name _____
First Middle Last
Today's date _____

1. __ Reviewed the Hypoglycemia Patient Questionnaire
2. __ Questioned the patient about circumstances surrounding severe or moderate hypoglycemia
3. __ Discussed strategies to avoid hypoglycemia with the patient
4. __ Made medication changes where clinically appropriate
5. __ Recommended carrying snack and/or glucose tablets where appropriate and provided instructions for how to use them (take 15 g glucose, wait 15 min, and remeasure blood glucose; repeat if hypoglycemia persists). A 1-page patient handout on treating hypoglycemia is available at http://clinical.diabetesjournals.org/content/30/1/38
6. __ Prescribed glucagon if appropriate

What are the current knowledge gaps in our understanding of hypoglycemia, and what research is necessary to fill these gaps?—Since the publication of the previous report from the Workgroup on Hypoglycemia in 2005 (1), much has been learned about the impact of hypoglycemia on patient outcomes. However, hypoglycemia continues to cause considerable morbidity and even mortality in patients with diabetes. If patients are to benefit from the reduction in microvascular complications that follows from achieving near-normal levels of glycemia, additional research will be necessary to prevent them from experiencing hypoglycemia and HAAF. First, new surveillance methods that provide consistent ways of reporting hypoglycemia must be developed so that the impact of any intervention to prevent and treat hypoglycemia can be fully assessed. Greater attention must be focused on understanding which patients are most at risk for hypoglycemia and on developing new educational strategies that effectively reduce the number of episodes experienced by at-risk patients. New therapies that do not cause hypoglycemia, including an artificial pancreas, need to be developed for both type 1 and type 2 diabetes. The technologies used to monitor blood glucose must become more accurate, more reliable, easier to use, and less expensive. The mechanisms that render patients unable to increase glucagon secretion in response to hypoglycemia and that are responsible for the development of HAAF must be identified so strategies can be developed to ensure that patients always experience early warning signs of impending neuroglycopenia. The impact of hypoglycemia on short-term outcomes such as mortality and long-term outcomes such as cognitive dysfunction need to be better defined, and the mechanisms for these associations need to be understood. Focused research in these priority areas will address our knowledge gaps about hypoglycemia and ultimately reduce the impact of iatrogenic hypoglycemia on patients with diabetes.

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