Hypoglycemia in Diabetes

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Iatrogenic hypoglycemia causes recurrent morbidity in most people with type 1 diabetes and many with type 2 diabetes, and it is sometimes fatal. The barrier of hypoglycemia generally precludes maintenance of euglycemia over a lifetime of diabetes and thus precludes full realization of euglycemia's long-term benefits. While the clinical presentation is often characteristic, particularly for the experienced individual with diabetes, the neurogenic and neuroglycopenic symptoms of hypoglycemia are nonspecific and relatively insensitive; therefore, many episodes are not recognized. Hypoglycemia can result from exogenous or endogenous insulin excess alone. However, iatrogenic hypoglycemia is typically the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in type 1 and advanced type 2 diabetes. Decrements in insulin, increments in glucagon, and, absent the latter, increments in epinephrine stand high in the hierarchy of redundant glucose counterregulatory factors that normally prevent or rapidly correct hypoglycemia. In insulin-deficient diabetes (exogenous) insulin levels do not decrease as glucose levels fall, and the combination of deficient glucagon and epinephrine responses causes defective glucose counterregulation. Reduced sympathoadrenal responses cause hypoglycemia unawareness. The concept of hypoglycemia-associated autonomic failure in diabetes posits that recent antecedent hypoglycemia causes both defective glucose counterregulation and hypoglycemia unawareness. By shifting glycemic thresholds for the sympathoadrenal (including epinephrine) and the resulting neurogenic responses to lower plasma glucose concentrations, antecedent hypoglycemia leads to a vicious cycle of recurrent hypoglycemia and further impairment of glucose counterregulation. Thus, short-term avoidance of hypoglycemia reverses hypoglycemia unawareness in most affected patients. The clinical approach to minimizing hypoglycemia while improving glycemic control includes *1*) addressing the issue, *2*) applying the principles of aggressive glycemic therapy, including flexible and individualized drug regimens, and *3*) considering the risk factors for iatrogenic hypoglycemia. The latter include factors that result in absolute or relative insulin excess: drug dose, timing, and type; patterns of food ingestion and exercise; interactions with alcohol and other drugs; and altered sensitivity to or clearance of insulin. They also include factors that are clinical surrogates of compromised glucose counterregulation: endogenous insulin deficiency; history of severe hypoglycemia, hypoglycemia unawareness, or both; and aggressive glycemic therapy per se, as evidenced by lower HbA_{1c} levels, lower glycemic goals, or both. In a patient with hypoglycemia unawareness (which implies recurrent hypoglycemia) a 2- to 3-week period of scrupulous avoidance of hypoglycemia is advisable. Pending the prevention and cure of diabetes or the development of methods that provide glucose-regulated insulin replacement or secretion, we need to learn to replace insulin in a much more physiological fashion, to prevent, correct, or compensate for compromised glucose counterregulation, or both if we are to achieve near-euglycemia safely in most people with diabetes.

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Abbreviations: DCCT, Diabetes Control and Complications Trial; HAAF, hypoglycemia-associated autonomic failure; PET, positron emission tomography; SMBG, self-monitoring of blood glucose; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Were it not for the barrier of hypoglycemia, people with diabetes could have normal HbA_{1c} levels over a lifetime of diabetes (1). It is now well-established that glycemic control makes a difference for people with diabetes. Reduction of mean glycemia over time prevents or delays microvascular complications—retinopathy, nephropathy, and neuropathy—in both type 1 (2) and type 2 diabetes (2–4). It may also reduce macrovascular events (2–4). However, iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes (1).

Glucose is an obligate metabolic fuel for the brain (5). Because the brain cannot synthesize glucose or store more than a few minutes' supply as glycogen, it is critically dependent on a continuous supply of glucose from the circulation. At normal (or elevated) arterial glucose concentrations, the rate of blood-to-brain glucose transport exceeds the rate of brain glucose metabolism. However, as arterial glucose levels fall below the physiological range, blood-to-brain glucose transport becomes limiting to brain glucose metabolism, and ultimately survival. Were it not for the potentially devastating effects of hypoglycemia on the brain, the glycemic management of diabetes would be rather straightforward. Enough insulin, or any effective drug, to lower plasma glucose concentrations to or below the physiological range would eliminate the symptoms of hyperglycemia, prevent the acute hyperglycemic complications (ketoacidosis, hyperosmolar syndrome), almost assuredly prevent the long-term microvascular complications (2–4), and likely reduce macrovascular risk (6,7). But the effects of hypoglycemia on the brain are real, and the glycemic management of diabetes is therefore complex and generally only partially successful.

Iatrogenic hypoglycemia often causes recurrent physical morbidity, recurrent or persistent psychosocial morbidity, or both and sometimes causes death (5). Furthermore, it precludes true glycemic control, i.e., maintenance of euglycemia over a lifetime, in the vast majority of people with diabetes (5). As a result, complications can occur despite aggressive therapy. For example, microvascular

complications developed in patients with type 1 diabetes (2) and those with type 2 diabetes (3,4) randomized to intensive glycemic therapy, albeit at lower rates than those assigned to less aggressive therapy. Indeed, the barrier of hypoglycemia may explain why aggressive attempts to achieve glycemic control have had little impact on macrovascular complications (2–4). It appears that the curve describing the relationship between mean glycemia (HbA_{1c}) and macrovascular events, such as myocardial infarction, is shifted toward lower glycemia than that between mean glycemia and microvascular complications (6). This is supported by evidence of an increased risk of death from ischemic heart disease in people with glycated hemoglobin levels in the high normal range (7). Thus, while it is possible to reduce mean glycemia enough to decrease the incidence of microvascular complications (2–4), perhaps it is not possible, with current treatment regimens, to hold plasma glucose concentrations low enough long enough to prevent macrovascular disease in a substantial proportion of people with diabetes because of the attendant risk of frequent and/or severe hypoglycemia. It is, of course, also plausible that the increased atherosclerotic risk conferred by diabetes is the result of factors in addition to or other than hyperglycemia.

Pending the prevention and cure of diabetes, people with diabetes need treatment methods that provide glucose-regulated insulin replacement or secretion if they are to consistently achieve and maintain euglycemia safely (1). Absent that, they and their caregivers must practice hypoglycemia risk reduction as they attempt to improve glycemic control while minimizing the risk of iatrogenic hypoglycemia (8).

FREQUENCY AND CLINICAL IMPACT OF IATROGENIC HYPOGLYCEMIA

Type 1 diabetes

Hypoglycemia is a fact of life for people with type 1 diabetes. Those attempting to improve or maintain glycemic control suffer untold numbers of episodes of asymptomatic hypoglycemia; plasma glucose levels may be less than 50–60 mg/dl (2.8–3.3 mmol/l) 10% of the time (5,9,10). They suffer an average of two episodes of symptomatic hypoglycemia per week—thousands of such episodes over a lifetime of diabetes—and an episode of severe, at least temporarily disabling, hypoglycemia approximately once a year (2,11,12). An estimated 2–4% of deaths of people with type 1 diabetes have been attributed to hypoglycemia (5,13).

The physical morbidity of an episode of hypoglycemia (5) ranges from unpleasant symptoms, such as anxiety, palpitations, tremor, sweating, hunger, and paresthesias, to neurological impairments, including behavioral changes, cognitive dysfunction, seizures, and coma. Focal neurological deficits occur occasionally. Although severe prolonged hypoglycemia can cause permanent brain damage, seemingly complete recovery is the rule.

At the very least, an episode of hypoglycemia is a nuisance and a distraction. It can be embarrassing and cause social ostracism. The psychological morbidity of hypoglycemia (5) includes fear of hypoglycemia, guilt about that rational fear, high levels of anxiety, and low levels of overall happiness. In her book about her life with type 1 diabetes Lisa Roney (14) wrote, "[T]hese episodes [of hypoglycemia] shame and haunt me, the most apparent shadow on my semblance of a normal life." Clearly, hypoglycemia is often a psychological, as well as a pathophysiological, barrier to glycemic control.

Finally, as noted earlier, to the extent it precludes glycemic control, hypoglycemia limits full realization of glycemic control's long-term benefits in type 1 diabetes (2).

Type 2 diabetes

While it is difficult to assess the absolute rates, the frequency of iatrogenic hypoglycemia is substantially lower in type 2 than in type 1 diabetes. Representative event rates for severe hypoglycemia (that requiring the assistance of another individual) during aggressive insulin therapy in type 1 diabetes range from 62 (2) through 110 (11) to 170 (12) episodes per 100 patient-years. Those during aggressive insulin therapy in type 2 diabetes range from 3 (15) through 10 (16) to 73 (12) episodes per 100 patient-years. Thus, the rates of severe hypoglycemia in type 2 diabetes are roughly 10% of those in type 1 diabetes even during aggressive therapy with insulin. They are undoubtedly even lower in those treated with oral hypoglycemic agents. However, quantitative data (i.e., event rates) from patients with type 2 diabetes treated to near-euglycemia with rigorous ascertainment of hypoglycemia are not available. Over 6 years of follow-up of patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS), 2.4% of those using metformin, 3.3% of those using a sulfonylurea, and 11.2% of those using insulin reported major hypoglycemia (that requiring medical attention or admission to hospital) (17). For comparison, 65% of the intensively treated patients with type 1 diabetes in the Diabetes Control and Complications Trial (DCCT) suffered severe hypoglycemia (that requiring the assistance of another individual) over 6.5 years of follow-up (2). Since the UKPDS involved newly diagnosed type 2 diabetes and the patients' glycemic control was not as strict as in the DCCT, the UKPDS data may well underestimate the frequency of iatrogenic hypoglycemia in type 2 diabetes.

Hypoglycemia became progressively more limiting to glycemic control over time in the UKPDS (17,18). Indeed, the UKPDS investigators noted that "patients often did not achieve normoglycemia. This was in part because of the high incidence of insulin-induced hypoglycemia, which is a limitation in treating patients with type 2 diabetes just as it is in patients with type 1 diabetes" (18). Furthermore, in one series, the frequencies of severe hypoglycemia were similar in type 2 and type 1 diabetes matched for duration of insulin therapy (19). Given progressive insulin deficiency in type 2 diabetes (17), these findings (17–19) indicate that iatrogenic hypoglycemia becomes a progressively more frequent clinical problem for patients with type 2 diabetes as they approach the insulin-deficient end of the spectrum.

Although the episodes are much less frequent overall, the physical and psychosocial morbidity of hypoglycemia in type 2 diabetes is reasonably assumed to be similar to that in type 1 diabetes summarized earlier. Reliable estimates of hypoglycemic mortality rates in type 2 diabetes are not available. However, deaths caused by sulfonylurea-induced hypoglycemia have been documented (20,21).

CLINICAL MANIFESTATIONS OF HYPOGLYCEMIA

Symptoms

Falling plasma glucose concentrations cause an array of symptoms by signaling central nervous system–mediated autonomic nervous system responses and by limiting neuronal metabolism. Neurogenic (or autonomic) symptoms are the result of the perception of physiological changes caused by the activation of the autonomic nervous system triggered by hypoglycemia (5,22,23). Although all three efferent components of the autonomic nervous system—adrenomedullary, sympathetic neural, and parasympathetic neural—are activated by hypoglycemia, neurogenic symptoms are thought to be caused by sympathoadrenal activation and mediated by norepinephrine released from sympathetic adrenergic postganglionic neurons, the adrenal medullae, or both, by acetylcholine released from cholinergic sympathetic postganglionic neurons and by epinephrine released from the adrenal medullae (22). Some neurogenic symptoms, such as tremulousness, palpitations, and anxiety/arousal, are adrenergic (catecholamine mediated); whereas others, such as sweating, hunger, and paresthesias, are cholinergic. Awareness of hypoglycemia is largely the result of the perception of neurogenic symptoms and the recognition that they are indicative of hypoglycemia (22). Clearly, therefore, awareness of hypoglycemia is a function of the knowledge and the experience of the individual, as well as the physiological responses to low glucose concentrations.

Neuroglycopenic symptoms are the result of brain neuronal glucose deprivation (5,22,23). They include sensations of warmth, weakness, and fatigue as well as difficulty thinking, confusion, behavioral changes (not infrequently confused with inebriation by others), and emotional lability. They also include seizures, loss of consciousness, and, if hypoglycemia is severe and prolonged, brain damage and even death.

Signs

Physical signs that result from activation of the sympathoadrenal system include pallor and diaphoresis, which are often prominent, and an increased heart rate and systolic blood pressure, which are often more subtle (5). Evidence of neuroglycopenia can be the most apparent, or even the only, observable manifestation of hypoglycemia. Indeed, the neuroglycopenic symptoms are often the clues recognized by family and friends of the affected individual. Hypothermia is often present. Transient focal neurological deficits (e.g., diplopia, hemiparesis) occur occasionally. As noted earlier, permanent brain damage is rare.

Diagnosis

While the clinical presentation can be characteristic, particularly for the experienced individual with diabetes, the symptoms and signs of hypoglycemia are nonspecific. Therefore, documentation of a low plasma or blood glucose concentration, if possible, is very helpful (5). Indeed, a hypoglycemic episode is most convincingly documented by Whipple's triad: symptoms compatible with hypoglycemia, a low plasma or blood glucose concentration, and resolution of those symptoms after the glucose concentration is raised to normal.

Symptoms of hypoglycemia are idiosyncratic and not infrequently unique to a given individual (23). Thus, many people with diabetes learn their unique symptoms based on their experience. While documentation of a low plasma or blood glucose concentration is preferable, if that is not practical it is better for the patient to self-treat when he or she suspects hypoglycemia, since the short-term risks of failure to treat an episode far outweigh those of unnecessary treatment.

Symptoms of hypoglycemia may occur but not be recognized as indicative of hypoglycemia, particularly when the patient's attention is focused on other issues. For example, some report that they are less likely to recognize hypoglycemia while at work than during leisure activities. Furthermore, the symptoms are relatively insensitive. In addition, many aggressively treated patients lose their symptoms and thus manifest the syndrome of hypoglycemia unawareness, as discussed below. For these reasons, many episodes, indeed the vast majority of episodes, are unrecognized or asymptomatic.

While plasma glucose concentrations can be unequivocally low, it is not possible to define hypoglycemia on the basis of a specific plasma glucose concentration in people with diabetes. As discussed later, the glycemic thresholds for responses to hypoglycemia have been defined, found to be reproducible from laboratory to laboratory, and used to define diagnostic criteria (5) in nondiabetic individuals. However, these thresholds are dynamic rather than static. People with poorly controlled diabetes can suffer symptoms of hypoglycemia at plasma glucose concentrations higher than those required to elicit symptoms in nondiabetic individuals (24,25), while those with tightly controlled (i.e., frequently hypoglycemic) diabetes often tolerate low glucose levels without symptoms (25). Nonetheless, the latter values cannot be ignored; lower glucose levels could cause episodes of clinical hypoglycemia. In practice, the self-monitored blood glucose levels that should be of concern need to be individualized for a given patient at a given point in time. Because lower levels impair defenses against subsequent hypoglycemia, as discussed below, a reasonable goal is a lower limit of ~72 mg/dl (4.0 mmol/l).

PHYSIOLOGY OF GLUCOSE COUNTERREGULATION

Glycemic thresholds

Decreasing plasma glucose concentrations normally elicit a characteristic sequence of responses (26–28):

1. Decreased insulin secretion as glucose concentrations decline within the physiological range. The physiological postabsorptive plasma glucose concentration range is ~72–108 mg/dl (4.0–6.0 mmol/l). The mean arterialized venous glycemic threshold for a decrease in insulin is ~81 mg/dl (4.5 mmol/l).
2. Increased glucagon and epinephrine secretion, among other neuroendocrine responses, as glucose concentrations fall just below the physiological range. The glycemic threshold is ~65–70 mg/dl (3.6–3.9 mmol/l).
3. Neurogenic and neuroglycopenic symptoms, and cognitive impairments, at lower plasma glucose concentrations. The glycemic threshold for symptoms is ~50–55 mg/dl (2.8–3.0 mmol/l).

While these glycemic thresholds are reproducible from laboratory to laboratory in healthy subjects (26–28), they shift to higher plasma glucose concentrations in

people with poorly controlled type 1 (24,25) and type 2 diabetes (29) and to lower plasma glucose concentrations in people with tightly controlled type 1 diabetes (25). These shifts are reflections of antecedent glycemia, chronic hyperglycemia and recent hypoglycemia respectively. For example, the glycemic thresholds are shifted to lower plasma glucose concentrations not only in tightly controlled (i.e., frequently hypoglycemic) diabetes (25) but also in patients with recurrent hypoglycemia caused by an insulinoma (30) and following induced hypoglycemia in both type 1 (31) and type 2 diabetes (29). As discussed shortly, these threshold shifts are quite relevant to the pathophysiology of glucose counterregulation in diabetes.

The magnitude of the neuroendocrine responses to hypoglycemia is a function of the nadir plasma glucose concentration, not the rate of fall of plasma glucose. During experimental insulin-induced hypoglycemia, insulin levels influence the magnitude of the responses; higher insulin levels restrain the glucagon response and enhance the catecholamine response. In general, women exhibit a less vigorous response to a given level of hypoglycemia than men.

Glycemic mechanisms

The mechanisms of this integrated neuroendocrine response to hypoglycemia and of the glycemic (plasma glucose–raising) actions of its components have been reviewed previously (5,32). Therefore, they are only summarized here.

Falling plasma glucose concentrations are detected by glucose-responsive neurons in the hypothalamus and other regions of the brain. There is evidence that they are also sensed in visceral sites, including the portal vein, and signaled to the central nervous system via the cranial nerve (parasympathetic afferent) visceral sensory system, specifically the vagus nerves, although signaling via the spinal nerve (sympathetic afferent) visceral sensory system has not been excluded. As a result of complex integration within the brain, these signals ultimately cause a patterned autonomic response organized within the hypothalamus and involving centers in the brain stem. Thus, hypoglycemia triggers increased sympathetic—sympathetic neural and adrenomedullary (sympathoadrenal)—and parasympathetic outflow from the central nervous system. Through hypothalamo-hypophyseal neuroendocrine mechanisms, hypoglycemia also causes increased adenohypophysial growth hormone and adrenocorticotropin (and thus adrenocortical cortisol) secretion, among other pituitary hormone responses. Finally, through mechanisms that include, but are not limited to, increased autonomic activity, hypoglycemia causes reduced pancreatic β-cell insulin secretion and increased pancreatic α-cell glucagon secretion.

Although insulin secretion is modulated by an array of substrate, neural, and hormonal factors, the dominant factor is the β-cell arterial glucose concentration. As plasma glucose concentrations decline, insulin secretion drops sharply; insulin secretion virtually ceases during hypoglycemia. α_2-Adrenergic inhibition of insulin secretion, resulting from sympathoadrenal activation, may also play a role. The mechanisms of the glucagon secretory response to hypoglycemia are less well understood. They include increased autonomic—parasympathetic neural, sympathetic neural, and adrenomedullary—inputs, a low α-cell arterial glucose concentration, and decreased intraislet insulin, but the relative contribution of these remains a matter of some debate (32).

The net result of these decrements in insulin secretion, increments in glucagon secretion, and autonomic and pituitary activations triggered by hypoglycemia includes increased endogenous glucose production, limited glucose utilization by tissues other than the brain, increased lipolysis, and increased proteolysis, as well as increased sweating and cutaneous vasoconstriction but net vasodilation, with increments in systolic blood pressure and heart rate. Their glycemic actions and their relative contributions to physiological defense against hypoglycemia are discussed in the paragraphs that follow.

Defense against hypoglycemia

Glucose counterregulation—the physiological mechanisms that normally prevent or rapidly correct hypoglycemia so effectively that hypoglycemia is a distinctly uncommon clinical event in people who do not have diabetes—has been reviewed in detail (32). Decreased insulin secretion, which favors increased hepatic (and renal) glucose production and decreased glucose utilization by insulin-sensitive tissues such as muscle, is the initial defense against falling plasma glucose concentrations. Among the glucose counterregulatory factors, increased glucagon secretion, which stimulates hepatic glycogenolysis and favors hepatic gluconeogenesis, plays a primary role. Albeit demonstrably involved, increased epinephrine secretion—which stimulates hepatic glycogenolysis and gluconeogenesis (and renal gluconeogenesis), the latter largely by mobilizing gluconeogenic substrates such as amino acids, lactate, and glycerol, and limits glucose utilization by insulin-sensitive tissues through mechanisms that include increased nonesterified fatty acid levels as well as direct effects—is not normally critical. However, it becomes critical when glucagon secretion is deficient. Glucagon and epinephrine act rapidly (within minutes) to raise plasma glucose concentrations. Increased secretion of cortisol and growth hormone, both of which limit glucose utilization by insulin-sensitive tissues and support glucose production over a longer time frame (hours), is involved in defense against prolonged hypoglycemia; but cortisol and growth hormone are not critical to recovery from even prolonged hypoglycemia or to the prevention of hypoglycemia after an overnight fast. To the extent it is involved, glucose autoregulation (endogenous glucose production as an inverse function of ambient plasma glucose concentrations independent of hormonal and neural glucoregulatory mechanisms) appears to play a relatively minor role.

Thus, insulin, glucagon, and epinephrine stand high in the hierarchy of redundant glucose counterregulatory factors. The secretion of all three of these hormones, not just insulin, is typically impaired in type 1 diabetes (1,5).

PATHOPHYSIOLOGY OF GLUCOSE COUNTERREGULATION IN DIABETES

Type 1 diabetes

Absolute or relative therapeutic (exogenous) insulin excess causes plasma glucose concentrations to fall to low levels in type 1 diabetes. As glucose levels decline, insulin concentrations do not decrease; these levels of insulin are unregulated and are simply the result of the passive absorption of the administered insulin and its pharmacokinetics. Thus, the first de-

fense against hypoglycemia is lost in established (i.e., C-peptide–negative) type 1 diabetes. Furthermore, as glucose levels fall, glucagon secretion does not increase in established type 1 diabetes (33,34). This is a signaling defect; glucagon secretory responses to stimuli other than hypoglycemia are largely, if not entirely, intact. The mechanism of the absent glucagon response to hypoglycemia that characterizes established type 1 diabetes is not known, but it is linked tightly to (35), and is possibly the result of (36), endogenous insulin deficiency. Thus, both the first and the second defenses against developing hypoglycemia are lost in established type 1 diabetes. These patients, therefore, rely to a greater extent on the third defense, increased epinephrine secretion. However, the epinephrine secretory response to falling glucose levels is typically attenuated in type 1 diabetes (25,31,34). The glycemic threshold for the epinephrine response is shifted to a lower plasma glucose concentration (25,31), largely the result of recent antecedent hypoglycemia (31). In summary, all three defenses against developing hypoglycemia—decrements in insulin, increments in glucagon, and increments in epinephrine—are typically impaired in established type 1 diabetes.

The reduced epinephrine response to a given level of hypoglycemia that characterizes type 1 diabetes (25,31,34) is largely, if not exclusively, a functional disorder rather than the result of a structural abnormality of the adrenal medullae (1,5). It is readily demonstrable in patients with type 1 diabetes who do not have classic diabetic autonomic neuropathy as assessed by cardiovascular reflex tests, orthostatic changes in blood pressures and heart rates, and clinical histories (31,37,38). However, there appears to be an additional effect of autonomic neuropathy. The epinephrine response has been found to be reduced to a somewhat greater extent in those with, compared with those without, classic diabetic autonomic neuropathy, at least at very low plasma glucose concentrations (31,37,38).

Type 2 diabetes

As noted earlier, iatrogenic hypoglycemia is much less frequent overall in type 2 diabetes. Glucose counterregulatory mechanisms have generally been found to be intact early in the course of type 2 diabetes (1,29). This likely explains the low frequency of hypoglycemia. However, as also noted above, iatrogenic hypoglycemia becomes progressively more limiting to glycemic control over time (17,18), and the frequencies of severe iatrogenic hypoglycemia have been reported to be similar in type 2 and type 1 diabetes matched for duration of insulin therapy (19). Given progressive insulin deficiency in type 2 diabetes (17), these findings indicate that iatrogenic hypoglycemia becomes a progressively more frequent clinical problem as patients approach the insulin-deficient end of the spectrum of type 2 diabetes. Thus, it would be expected that such patients would exhibit glucose counterregulatory defects similar to those in type 1 diabetes. That expectation has been supported. Patients with advanced type 2 diabetes, selected for insulin deficiency, were found to have virtually absent glucagon secretory responses to hypoglycemia (29), and their glycemic thresholds for autonomic and symptomatic responses were shifted to lower plasma glucose concentrations following recent hypoglycemia (29).

CLINICAL SYNDROMES OF COMPROMISED GLUCOSE COUNTERREGULATION IN DIABETES

Defective glucose counterregulation

Patients with type 1 diabetes and combined deficiencies of their glucagon and epinephrine responses to hypoglycemia have been shown, in prospective studies, to be at 25-fold (39) or even higher (40) increased risk for severe iatrogenic hypoglycemia during aggressive glycemic therapy compared with those with absent glucagon but normal epinephrine responses. The combination of absent glucagon and attenuated epinephrine responses causes the clinical syndrome of defective glucose counterregulation (1,5).

It has been suggested that a factor or factors in addition to absent glucagon and attenuated epinephrine responses to hypoglycemia, perhaps impaired glucose autoregulation, may play a role in the pathogenesis of defective glucose counterregulation in type 1 diabetes (41). Glucagon secretion was suppressed with somatostatin (and replaced at basal rates), and plasma glucose was lowered with insulin to only ~70 mg/dl (3.9 mmol/l), which did not raise plasma epinephrine to biologically effective levels. With comparable plasma glucagon and epinephrine concentrations during this mild hypoglycemia, rates of endogenous glucose production were found to be ~20% lower in patients with type 1 diabetes than in nondiabetic control subjects.

Hypoglycemia unawareness

The attenuated epinephrine response to hypoglycemia in type 1 diabetes is a marker of an attenuated autonomic, sympathetic neural as well as adrenomedullary, response that causes the clinical syndrome of hypoglycemia unawareness—loss of the warning, largely neurogenic symptoms of developing hypoglycemia. Because it compromises behavioral defenses against developing hypoglycemia (e.g., the ingestion of food), hypoglycemia unawareness is also associated with a high frequency of severe iatrogenic hypoglycemia (42).

Hypoglycemia unawareness is generally thought to be the result of reduced sympathoadrenal responses and the resultant reduced neurogenic symptom responses to a given level of hypoglycemia (1,5,43–45). Based on the finding of reduced cardiac chronotropic sensitivity to infused isoproterenol in patients with impaired awareness of hypoglycemia, it has been suggested that reduced β-adrenergic sensitivity might also be involved (46–49). Antecedent hypoglycemia has been reported to decrease sensitivity to isoproterenol in patients with type 1 diabetes, but to increase it in nondiabetic individuals (48).

Hypoglycemia-associated autonomic failure

The concept of hypoglycemia-associated autonomic failure (HAAF) in type 1 diabetes (1,31) and advanced type 2 diabetes (1,29) posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing the epinephrine response to subsequent hypoglycemia in the setting of an absent glucagon response) and hypoglycemia unawareness (by reducing the autonomic—sympathetic neural and adrenomedullary—response and thus the resulting neurogenic symptom responses to subsequent hypoglycemia) and thus a vicious cycle of recurrent hypoglycemia. The concept of HAAF is illustrated in Fig. 1.

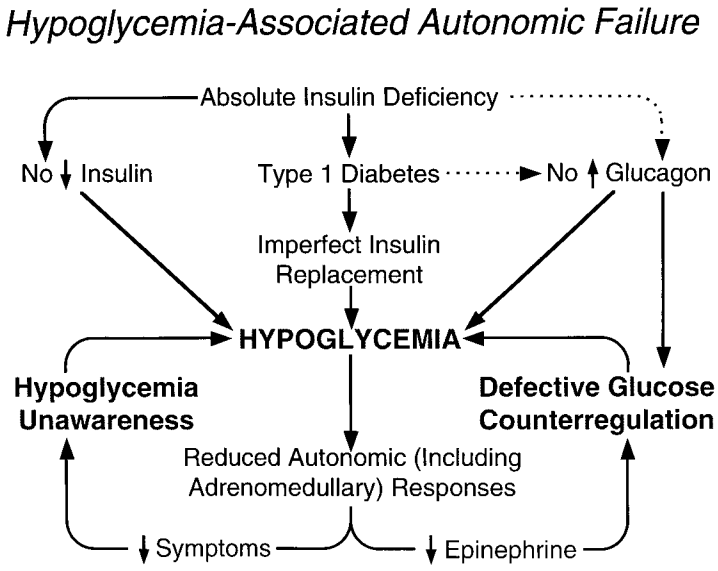

Figure 1—*Diagrammatic representation of the concept of hypoglycemia-associated autonomic failure in diabetes. Modified from Cryer (50).*

Conceived initially (50) on the basis of findings in nondiabetic individuals (51,52), the concept of HAAF now has considerable support in the clinical setting. In patients with type 1 diabetes, recent antecedent hypoglycemia has been shown to *1*) shift glycemic thresholds for autonomic (including epinephrine and symptomatic) and cognitive dysfunction responses to subsequent hypoglycemia to lower plasma glucose concentrations (31,53), *2*) impair glycemic defense against hyperinsulinemia (31), and *3*) reduce detection of hypoglycemia in the clinical setting (54). Perhaps the most compelling support for the clinical relevance of HAAF in type 1 diabetes is the finding, in three independent laboratories, that as little as 2–3 weeks of scrupulous avoidance of iatrogenic hypoglycemia reverses hypoglycemia unawareness and improves the reduced epinephrine component of defective glucose counterregulation in most affected patients (55–57). Notably, the absent glucagon response is not restored (55–57).

The mediators and mechanisms of HAAF are unknown. Detailed discussion of ongoing studies of these (1,58) is beyond the scope of this review. Briefly, based on the findings that cortisol infusion reduces sympathoadrenal responses to hypoglycemia the following day in healthy subjects (59) and that hypoglycemia in patients with primary adrenocortical failure does not reduce sympathoadrenal responses to hypoglycemia the following day (60), it has been suggested that it is the cortisol response to antecedent hypoglycemia that mediates HAAF. In support of that suggestion, maximally (ACTH) stimulated endogenous cortisol secretion has been shown to reduce the sympathoadrenal and neurogenic symptom responses to hypoglycemia the following day (61). However, it remains to be documented that prior cortisol elevations comparable to those that occur during hypoglycemia reproduce the HAAF phenomenon. There is evidence, using the Kety-Schmidt technique, that brain glucose uptake is preserved during hypoglycemia after prolonged (56-h) interprandial hypoglycemia in healthy subjects (62) and in patients with well-controlled (i.e., frequently hypoglycemic) type 1 diabetes (63). However, ~24 h of interprandial hypoglycemia was not found to increase global blood-to-brain glucose transport measured with [1-^{11}C]glucose and positron emission tomography (PET) or cerebral blood flow measured with [^{15}O]water and PET (64). The latter findings do not support the possibility that increased global blood-to-brain glucose transport is the mechanism of HAAF, but they do not exclude regional increments. A difference in the subthalamic handling of ^{18}F-labeled deoxyglucose, measured with PET, in patients with hypoglycemia awareness and unawareness has been reported (65).

CLINICAL RISK FACTORS FOR HYPOGLYCEMIA IN DIABETES

Insulin excess alone

The conventional risk factors for iatrogenic hypoglycemia (1,5) are based on the premise that absolute or relative insulin excess, whether from injected or from secreted insulin, is the sole determinant of risk. Absolute or relative insulin excess occurs when

1. Insulin (or insulin secretagogue or sensitizer) doses are excessive, ill-timed, or of the wrong type.
2. Exogenous glucose delivery is decreased, such as after missed meals or snacks and during the overnight fast.
3. Endogenous glucose production is decreased, such as following alcohol ingestion.
4. Glucose utilization is increased, such as during exercise.
5. Sensitivity to insulin is increased, such as late after exercise, in the middle of the night, and after weight loss, increased fitness, or improved glycemic control, or during treatment with an insulin sensitizer.
6. Insulin clearance is decreased, such as with progressive renal failure.

Although each must be considered carefully, these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia (66).

Insulin excess plus compromised glucose counterregulation

Iatrogenic hypoglycemia is more appropriately viewed as the result of the interplay of absolute or relative insulin excess and compromised glucose counterregulation in type 1 and advanced type 2 diabetes (1,5). In other words, although substantial insulin excess can cause hypoglycemia, the integrity of the physiological and behavioral defenses against falling plasma glucose concentrations determines if less-marked hyperinsulinemia, which must occur from time to time because of the pharmacokinetic imperfections of current insulin replacement regimens, causes an episode of hypoglycemia. Risk factors relevant to compromised glucose counterregulation that are well-established in type 1 diabetes (1,2, 35,67,68) and are likely relevant to advanced type 2 diabetes include: *1)* insulin

deficiency; 2) history of severe hypoglycemia, hypoglycemia unawareness, or both; 3) aggressive glycemic therapy per se, as evidenced by lower HbA_{1c} levels, lower glycemic goals, or both. These are clinical surrogates of the key features of the pathophysiology of glucose counterregulation discussed earlier. Insulin deficiency indicates that insulin levels will not decrease and predicts accurately that glucagon levels will not increase normally (33–35) as plasma glucose concentrations fall. A history of severe hypoglycemia indicates, and that of hypoglycemia unawareness or even aggressive glycemic therapy per se implies, recent antecedent hypoglycemia. The latter is the proximate cause of HAAF (Fig. 1) and the resulting vicious cycle of recurrent iatrogenic hypoglycemia.

An association between the ACE DD genotype/serum ACE activity phenotype and severe hypoglycemia in patients with type 1 diabetes has been reported (69). However, that was apparent only with very high serum ACE activities and was weak compared with the association with well-established risk factors for severe hypoglycemia, such as C-peptide negativity, hypoglycemia unawareness, and lower HbA_{1c} levels (69). Furthermore, there was no association between the ACE genotype/phenotype and symptomatic (as opposed to severe) hypoglycemia, the proportion of patients suffering severe hypoglycemia, or the frequency of hypoglycemia unawareness. Finally, a plausible mechanism of the association is not apparent.

CLINICAL APPROACH TO THE PROBLEM OF IATROGENIC HYPOGLYCEMIA

Treatment

Episodes of asymptomatic hypoglycemia (detected by self-monitoring of blood glucose [SMBG]) and most episodes of symptomatic hypoglycemia can be effectively self-treated by ingestion of glucose tablets or carbohydrate in the form of juice, a soft drink, milk, crackers, or a meal. An initial glucose dose of 20 g is reasonable (70). This should be repeated in 15–20 min if symptoms have not improved or the monitored blood glucose remains low. However, the glycemic response to oral glucose is transient, typically <2 h (70). Therefore, ingestion of a snack or meal shortly after the plasma glucose concentration is raised is generally advisable.

Parenteral therapy is necessary when a hypoglycemic patient is unable or unwilling (because of neuroglycopenia) to take carbohydrate orally (5,8). Parenteral glucagon is often used by family members to treat hypoglycemia in type 1 diabetes. Glucagon is less useful in type 2 diabetes because it stimulates insulin secretion as well as glycogenolysis. Intravenous glucose is the preferable treatment of severe hypoglycemia. Because severe hypoglycemia, particularly that caused by a sulfonylurea, is often prolonged in type 2 diabetes, subsequent glucose infusion and frequent feedings are often required. It is important to establish the absence of recurrent hypoglycemia unequivocally before such a patient is discharged.

Prevention

Obviously, prevention of hypoglycemia is preferable to its treatment. It is possible to improve glycemic control while minimizing the risk of hypoglycemia (8,71). Reducing the risk of hypoglycemia, while attempting to hold plasma glucose concentrations as close to the nondiabetic range as can be accomplished safely, involves three steps: *1*) addressing the issue of hypoglycemia in each patient contact; *2*) applying the principles of aggressive therapy; *3*) considering both the conventional risk factors and those indicative of compromised glucose counterregulation.

The issue of hypoglycemia should be addressed in each patient contact. Is the patient having episodes of hypoglycemia, and is he or she aware of hypoglycemia? Are these episodes severe? When do they occur? What is the temporal relation to drug administration, meals and snacks, alcohol use, and exercise? How low are the SMBG values that are associated with symptoms? Are there low values in the SMBG log? Do family members think episodes are occurring that are not recognized by the patient? To what extent is the patient concerned about actual or possible hypoglycemia? Obviously, one cannot solve the problem of iatrogenic hypoglycemia if it is not recognized to be a problem.

The principles of aggressive glycemic therapy include *1*) patient education and empowerment, *2*) frequent SMBG, *3*) flexible insulin and other drug regimens, *4*) individualized glycemic goals, and *5*) ongoing professional guidance and support (5,8).

A well-informed person with the ability and willingness to take charge of his or her diabetes is key to successful glycemic management, including the prevention of hypoglycemia. Does the patient understand the time course of the drugs he or she is using; the impact of food, exercise, and other drugs, including alcohol; and the symptoms of hypoglycemia, including his or her unique symptoms? Does he or she know how to respond to low SMBG values? Does he or she perform SMBG appropriately and use pattern recognition to refine the regimen? What is the meal plan, and does it include snacks? Does he or she do SMBG before performing critical tasks such as driving?

Obviously, with a history of recurrent hypoglycemia, one should identify plausible causes and adjust the regimen accordingly. In a patient treated with basal-bolus insulin, morning fasting hypoglycemia implicates the long- or intermediate-acting insulin; daytime hypoglycemia implicates the rapid or short-acting insulin; nocturnal hypoglycemia may implicate either. Substitution of a preprandial rapid-acting insulin analogue (e.g., lispro or aspart) for short-acting (regular) insulin reduces the frequency of nocturnal hypoglycemia (72–74). Substitution of a long-acting insulin analogue (e.g., glargine or detemir) for intermediate-acting insulin (NPH or ultralente) may also reduce the frequency of nocturnal hypoglycemia (75–77). With a continuous subcutaneous infusion regimen using a rapid-acting insulin, nocturnal and morning fasting hypoglycemia implicate the basal insulin infusion rate whereas daytime hypoglycemia may implicate the preprandial insulin bolus doses, the basal insulin infusion rate, or both.

Theoretically, monotherapy of type 2 diabetes with a biguanide, a thiazolidinedione, or an α-glucosidase inhibitor should not cause hypoglycemia. Patients responsive to these drugs must have endogenous insulin secretion, and insulin secretion should decrease appropriately as the plasma glucose concentration falls. Nonetheless, hypoglycemia, including major hypoglycemia, has been reported with metformin (17). In patients using a sulfonylurea, hypoglycemia is more often reported in those using long-acting agents, such as chlorpropamide or gly-

buride (glibenclamide) (20,21,78). The frequency of hypoglycemia in patients using rapid-acting insulin secretagogues, such as repaglinide or nateglinide, remains to be determined, although these drugs are thought largely to enhance glucose-stimulated insulin secretion. In one trial, only 23% of patients treated to a mean HbA_{1c} of ~6.3% with nateglinide reported symptoms of hypoglycemia, and none reported severe hypoglycemia (79).

The extent to which the frequency of iatrogenic hypoglycemia in type 2 diabetes is a function of the specific glucose-lowering drug used or the stage of the disease is not entirely clear. Is the higher frequency of hypoglycemia in patients treated with insulin the result of its greater glucose-lowering potency (given in sufficient doses) and its pharmacokinetic imperfections, or is it because patients who require insulin have advanced insulin-deficient type 2 diabetes with the associated compromised glucose counterregulation (29) discussed earlier?

Specific factors that warrant consideration include meals, exercise, and alcohol intake, as well as age (5,8). Theoretically, the use of a rapid-acting insulin analogue, rather than regular insulin, before meals in a basal-bolus insulin regimen should reduce the likelihood of hypoglycemia before the next meal. Dosage adjustments based on the premeal SMBG value and carbohydrate counting should also reduce the risk of subsequent hypoglycemia. Because exercise increases glucose utilization, and vigorous exercise increases it several-fold, exercise-induced hypoglycemia is a not infrequent problem in drug-treated, particularly insulin-treated, diabetes. Planned exercise can be preceded by reduced insulin doses, based on the baseline SMBG level, and accompanied by carbohydrate ingestion. The latter is the only option during unplanned exercise. Exercise has been reported to reduce glucose counterregulatory responses to subsequent hypoglycemia to a greater (80) or lesser (81) degree. This may play a role in the pathogenesis of late postexercise hypoglycemia. Alcohol inhibits gluconeogenesis and is therefore more likely to contribute to the development of hypoglycemia when glycogen stores are low, e.g., during an overnight fast. Inebriation, of course, can impair all aspects of diabetes management. Issues particularly relevant to the risk of iatrogenic hypoglycemia in older individuals include inconsistent eating patterns and even malnutrition, renal insufficiency, and drug interactions, as well as consideration of the risk-to-benefit relationship.

The third step in hypoglycemia risk reduction is consideration of the risk factors discussed earlier. In addition to those that lead to absolute or relative insulin excess—insulin or other drug doses, timing, and type; patterns of food ingestion and exercise; interactions with alcohol or other drugs; altered sensitivity to, or clearance of, insulin—these include risk factors for compromised glucose counterregulation (1,2,35,67,68). The latter include insulin deficiency, which may be apparent from a history of ketosis-prone diabetes requiring therapy with insulin from the time of diagnosis, although it is now clear that insulin deficiency can develop more slowly in type 1 diabetes and that it does develop in type 2 diabetes. These risk factors also include a history of severe hypoglycemia, hypoglycemia unawareness, or both, as well as aggressive glycemic therapy per se, as evidenced by lower HbA_{1c} levels, lower glycemic goals, or both. A diagnosis of hypoglycemia unawareness (which also implies defective glucose counterregulation) can often be made from the history, and that diagnosis implies recurrent hypoglycemia. If recurrent hypoglycemia is not apparent to the patient or to his or her family and is not reflected in the patient's SMBG log, it is probably occurring during the night.

Iatrogenic hypoglycemia often occurs during the night (5,66,67), which is typically the longest interdigestive interval and the longest interval between SMBG and the time of maximal sensitivity to insulin (82). Furthermore, sleep often precludes recognition of warning symptoms of developing hypoglycemia and thus the appropriate behavioral responses. Sleep has also been reported to further reduce the epinephrine response to hypoglycemia (83). Approaches to the problem of nocturnal hypoglycemia include regimen adjustments, the use of rapid-acting insulin (e.g., lispro or aspart) during the day and of long-acting basal insulin (e.g., glargine or detemir), as mentioned earlier, and the use of bedtime snacks. However, the efficacy of the latter is largely limited to the first half of the night (84). Experimental approaches include bedtime administration of the glucagon-stimulating amino acid alanine, the epinephrine-simulating β_2-adrenergic agonist terbutaline, and the slowly digested carbohydrate uncooked cornstarch (8,81).

In patients with clinical hypoglycemia unawareness, a 2- to 3-week period of scrupulous avoidance of hypoglycemia is advisable and can be assessed by return of awareness of hypoglycemia. Although that has been accomplished without (55,56) or with minimal (57) compromise of glycemic control, it has required substantial involvement of health professionals. In practice it can involve acceptance of somewhat higher glucose levels in the short term. Nonetheless, with the return of symptoms of developing hypoglycemia, empirical approaches to better glycemic control can be tried.

PERSPECTIVE

Iatrogenic hypoglycemia is a short-term and long-term problem for people with type 1 diabetes and for many people with type 2 diabetes. The problem can be minimized but cannot be eliminated if the goal of treatment is near-euglycemia. Every effort needs to be made to minimize the frequency and magnitude of hypoglycemia. Severe hypoglycemia—that requiring the assistance of another person—is a clinical red flag. Unless it was the result of an easily remediable factor, such as a missed meal after insulin injection or vigorous exercise without the appropriate regimen adjustment, a substantive change in the regimen must be made. If a change is not made, the risk of recurrent severe hypoglycemia is unacceptably high (1,2,35,66,67).

The fundamental problem with current treatment regimens is that they do not provide plasma glucose–regulated insulin replacement or secretion. The time course of the glucose-lowering actions of subcutaneous insulin, even the shortest acting analogues, is measured in hours whereas that of endogenous insulin in nondiabetic individuals is measured in minutes. In addition to the imperfect pharmacokinetics of injected insulin, the pharmacodynamics of the sulfonylureas are such that they too can produce hyperinsulinemic hypoglycemia in responsive patients. It remains to be determined whether the newer rapid-acting insulin secretagogues (repaglinide and nateglinide) will only enhance glucose-stimulated insulin secretion with a correspondingly low rate of hypoglycemia in those patients who achieve glycemic control. Biguanides

should not produce hypoglycemia, although they have been reported to do so. However, given absolute insulin deficiency in type 1 diabetes and progressive insulin deficiency over time in type 2 diabetes, most people with diabetes will ultimately require treatment with insulin, even with its pharmacokinetic imperfections.

In theory, glucose-regulated insulin replacement might be accomplished by pancreatic islet transplantation, a bioengineered artificial β-cell or a closed-loop insulin-replacement system. With respect to the latter, a reliable glucose sensor is the missing component (84). Pending the prevention and cure of diabetes or the development of treatment methods that provide glucose-regulated insulin replacement or secretion, we need to learn to replace insulin in a much more physiological fashion; to prevent, correct, or compensate for compromised glucose counterregulation; or both if we are to achieve near-euglycemia safely in people with diabetes.

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