Hypoglycemia Unawareness in IDDM

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Hypoglycemia unawareness—loss of the neurogenic (autonomic) warning symptoms of developing hypoglycemia—is one of three hypoglycemia-associated clinical syndromes that exemplify hypoglycemia-associated autonomic failure in IDDM. Reduced awareness of developing hypoglycemia (an elevated glycemic threshold for symptoms) is a feature not only of hypoglycemia unawareness but also of the syndromes of defective glucose counterregulation, elevated glycemic thresholds for symptoms, and activation of glucose counterregulatory systems during effective intensive therapy. These syndromes are major risk factors for severe iatrogenic hypoglycemia in individuals with IDDM. Their pathogenesis is unknown and likely multifactorial. Recent antecedent iatrogenic hypoglycemia may be one factor, perhaps a major factor, that, by reducing both the symptoms of and defenses against developing hypoglycemia, results in recurrent iatrogenic hypoglycemia, thus creating a vicious cycle. On the other hand, treatment with human compared with animal insulin does not appear to be an important factor.

Hypoglycemia is a fact of life for individuals with IDDM (1–3). They suffer an average of one to two episodes of symptomatic hypoglycemia per week. Further, in a given year, 10–25% suffer at least one episode of severe, temporarily disabling hypoglycemia, often with seizure or coma. Not surprisingly, the frequency of iatrogenic hypoglycemia is a function of the intensity of treatment; it is inversely related to the median plasma glucose concentration (1). Four percent of deaths of individuals with IDDM have been attributed to hypoglycemia (1). In addition to this recurrent physical morbidity, and some mortality, the fear of developing severe hypoglycemia causes recurrent or even persistent psychological morbidity in many individuals with IDDM (1,3). Clearly, hypoglycemia is the limiting factor in the management of IDDM (1).

All insulin replacement regimens used to treat IDDM are imperfect compared with normal endogenous insulin secretion. Thus, hyperinsulinemia (as well as hypoinsulinemia) must occur from time to time in individuals with IDDM. Conventional risk factors for iatrogenic hypoglycemia are based on the premise that absolute or relative hyperinsulinemia is the sole determinant (1). This occurs when insulin doses are excessive or ill-timed; when the influx of exogenous glucose is reduced, as after missed meals or snacks and during an overnight fast; when endogenous glucose production is decreased, as after excessive alcohol ingestion; when insulin-independent glucose utilization is increased, as during physical exercise; when sensitivity to insulin is increased, as during effective intensive therapy or when the secretion of cortisol, growth hormone, or both are deficient; and when the clearance of exogenous insulin is reduced, as in renal failure. However, thorough analysis of a large number of episodes of severe iatrogenic hypoglycemia has disclosed that such conventional risk factors account for only a minority of episodes (2). Thus, attention has shifted to a second category of risk factors, those that compromise physiological or behavioral defenses against hyperinsulinemia (1,4). Obviously, hyperinsulinemia of sufficient magnitude will invariably cause hypoglycemia. However, glucose counterregulatory (plasma glucose-raising) systems normally prevent hypoglycemia, particularly severe symptomatic hypoglycemia, during less marked hyperinsulinemia (5). Thus, the relative integrity of the glucose counterregulatory systems determines whether mild to moderate hyperinsulinemia results in clinical hypoglycemia in individuals with IDDM.

Three pathophysiological conditions that compromise defenses against hyperinsulinemia and are associated with a high frequency of iatrogenic hypoglycemia in individuals with IDDM are now recognized. These are: 1) hypoglycemia unawareness (1,6–14); 2) defective glucose counterregulation attributable to the combined deficiencies of the glucagon and epinephrine secretory responses to falling plasma glucose concentrations (1,12,13,15–19); and 3) elevated glycemic thresholds (lower plasma glucose concentrations required) for symptoms and for activation of glucose counterregulatory systems during intensive therapy

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IDDM, insulin-dependent diabetes mellitus.

that effectively lowers overall plasma glucose concentrations (1,13,20–22). Because these hypoglycemia-associated clinical syndromes segregate together and share various pathophysiological features, including reduced autonomic—both sympathochromaffin (epinephrine) and parasympathetic (pancreatic polypeptide)—responses to a given degree of hypoglycemia, these syndromes are examples of hypoglycemia-associated autonomic failure in IDDM, a disorder distinct from diabetic autonomic neuropathy (4). It has been hypothesized that recent antecedent hypoglycemia may play a role in the pathogenesis of hypoglycemia-associated autonomic failure (4). Recent data support that hypothesis (23).

Hypoglycemia unawareness was the first of the hypoglycemia-associated clinical syndromes to be described, and is the subject of this article. This syndrome has been reviewed (24).

MECHANISMS OF NORMAL HYPOGLYCEMIA AWARENESS

AWARENESS— Nondiabetic individuals and most individuals with IDDM, at least early in the course of the disease, become aware of developing hypoglycemia because they learn to recognize typical (or idiosyncratic) symptoms that normally result, either indirectly or directly, from low plasma glucose concentrations. These symptoms are conventionally divided into two categories: neurogenic (or autonomic) and neuroglycopenic (25–27). Symptoms thought to be the result of an autonomic discharge triggered by hypoglycemia are preferably termed neurogenic (or autonomic) symptoms. The term adrenergic should not be used in the generic sense for this category of symptoms. Although many of the neurogenic symptoms are adrenergic (mediated by catecholamines released from the adrenal medulla and/or noradrenergic sympathetic postganglionic neurons), sweating, a common symptom of hypoglycemia, is cholinergic (mediated by acetylcholine released from cholinergic sympathetic postganglionic neurons) (14,27,28). In addition to sweating, hunger and paresthesia are cholinergic neurogenic symptoms whereas palpitations, tremor, and anxiety are adrenergic neurogenic symptoms (28). The extent to which the latter adrenergic symptoms are mediated by epinephrine secreted from the adrenal medulla and/or norepinephrine released from sympathetic nerves is not entirely clear. Considerable evidence indicates that epinephrine mediates many of the hemodynamic responses to hypoglycemia (27); thus, a symptom such as palpitations might well be mediated by the hormone. Indeed, it has been reported that all symptoms other than palpitations occur during hypoglycemia in splanchnicectomized (adrenal-medulla denervated) humans (29).

On the other hand, symptoms thought to be the direct result of neuronal fuel (glucose) deprivation are termed neuroglycopenic symptoms. Examples include difficulty concentrating, confusion, weakness, drowsiness, warmth, and perhaps slurred speech, dizziness, faintness, and blurred vision. Behavioral changes, seizures, and coma are also manifestations of neuroglycopenia. The ultimate result of severe, prolonged neuroglycopenia is death.

Because patients with cervical spinal cord transections (which interrupt brain-to-sympathochromaffin neural outflow) do not recognize hypoglycemia (30), it is reasonable to suggest that normal awareness of hypoglycemia is based largely, if not exclusively, on the perception of neurogenic symptoms (26,31). Indeed, recent data indicate that panautonomic (adrenergic and cholinergic) blockade prevents recognition of hypoglycemia in normal individuals (28). Clearly, however, if developing hypoglycemia is to be recognized, adequate cognitive function is required to interpret these symptoms as indicative of hypoglycemia, prompting the individual to respond appropriately. For example, alcohol ingestion has been shown to impair recognition of hypoglycemia by suppressing cognition (32). Thus, neuroglycopenia may well be the reason many patients fail to recognize neurogenic symptoms later recalled to have been present before a severe hypoglycemic episode (2). However, an alternative possibility, that at least some of those patients had not learned to recognize the appropriate neurogenic symptoms, cannot be excluded categorically.

It is now well documented that there is an order to the responses to hypoglycemia (33,34). In nondiabetic individuals, the glycemic threshold for activation of glucose counterregulatory systems (including glucagon and epinephrine secretion) is ~3.8 mM, for symptoms it is ~3.0 mM, and for cognitive dysfunction it is ~2.8 mM. Some (34), but not all (22,33), find the glycemic thresholds for neurogenic symptoms to be at slightly higher plasma glucose levels (~3.2 mM) than those for neuroglycopenic symptoms (~2.8 mM). As discussed later, however, these glycemic thresholds vary in patients with IDDM, at least in part in relation to antecedent glycemia.

CLINICAL HYPOGLYCEMIA UNAWARENESS IN IDDM

IDDM— In general, during the early years of IDDM, patients are able to recognize developing hypoglycemia, presumably on the basis of the neurogenic warning symptoms discussed earlier, and take appropriate action (e.g., eat) to prevent its progression to severe, temporarily or even permanently disabling neuroglycopenia. Over time, many patients fail to have (or perceive) these warning symptoms and therefore suffer recurrent severe hypoglycemia. That is, they develop clinical hypoglycemia unawareness (1,6–14). This process probably proceeds from awareness through a phase of partial awareness to frank unawareness (6,10).

Clinical hypoglycemia unawareness is not a newly recognized phenomenon. It was alluded to in early reports soon after the introduction of insulin

therapy (for review, see 24). Lawrence (6) described the syndrome clearly in 1941: "As years of insulin life go on, sometimes only after 5–10 years, I find it almost the rule that the type of insulin reaction changes, the premonitory autonomic symptoms are missed out and the patient proceeds directly to the more serious manifestations affecting the central nervous system."

The true prevalence of clinical hypoglycemia unawareness is not known. In a retrospective, cross-sectional study, Hepburn et al. (10) found that 7% of their patients reported complete hypoglycemia unawareness and an additional 16% reported partial unawareness. In another cross-sectional study, Pramming et al. (3) demonstrated a clear relationship between the frequency of hypoglycemia unawareness and the duration of IDDM (noted by Lawrence 50 years earlier [6]). Pramming et al. (3) found that the proportion of patients experiencing sweating and/or tremor (clear-cut neurogenic symptoms) during hypoglycemia decreased over time with IDDM, whereas the proportion of patients suffering severe hypoglycemic episodes without warning symptoms (hypoglycemia unawareness) increased over time with IDDM. After 30 years of IDDM, ~50% of their patients reported such episodes. It would seem likely that, because of the reliance on retrospective clinical reporting, the available data underestimate the frequency of hypoglycemia unawareness in IDDM.

Hepburn et al. (10) found ~10-fold increase in the incidence of severe hypoglycemia in patients reporting hypoglycemia unawareness. Severe hypoglycemia was reported by 91% of the patients with complete hypoglycemia unawareness, but by only 18% of those with complete awareness. Thus, although it has not, to my knowledge, been documented in prospective studies, it seems clear that hypoglycemia unawareness is a major risk factor for severe iatrogenic hypoglycemia in individuals with IDDM.

MECHANISMS OF HYPOGLYCEMIA UNAWARENESS IN IDDM— Accepting the premise that normal awareness of developing hypoglycemia is based on the perception of neurogenic warning symptoms (28), as discussed earlier, hypoglycemia unawareness in IDDM could theoretically be the result of a reduced autonomic response, a reduced end-organ sensitivity to a normal autonomic response, or both. Berlin et al. (35) have reported reduced cardiac chronotropic sensitivity to the β-adrenergic agonist isoproterenol in IDDM patients with clinical hypoglycemia unawareness. However, even if this phenomenon was shown to be generalized for all responses to adrenergic agonism, reduced adrenergic sensitivity could not explain all of the features of hypoglycemia unawareness. Reduced diaphoretic responses, which, as mentioned earlier, are cholinergic, would remain unexplained. Therefore, reduced autonomic responses to developing hypoglycemia are conceptually a more attractive explanation for hypoglycemia unawareness.

Hypoglycemia unawareness is associated with a reduced adrenomedullary epinephrine response to experimental hypoglycemia (8,9,11,13). Stated differently, the glycemic thresholds for epinephrine release (11,13), as well as for symptoms (13), are elevated in that lower plasma glucose concentrations are required to elicit this response. However, the complete syndrome could be adequately explained only if the reduced epinephrine response were a marker for a more generalized reduction of the autonomic response with reduced sympathetic (and perhaps parasympathetic) neural as well as adrenomedullary responses, because reduced sympathetic neural, but not reduced adrenomedullary activation, could also explain the reduced sweating and other cholinergic responses (26).

If hypoglycemia unawareness in IDDM is the result of a reduced autonomic response to a given degree of hypoglycemia, what is the mechanism of the reduced autonomic response? There is good reason to suspect that the mechanism is not classical diabetic autonomic neuropathy. First, hypoglycemia unawareness is not associated with classical diabetic autonomic neuropathy (10,12). For example, in the series of patients studied by Ryder et al. (12), none of the patients with hypoglycemia unawareness had classical diabetic autonomic neuropathy. Second, unlike hypoglycemia unawareness, classical diabetic autonomic neuropathy is not associated with an increased frequency of severe iatrogenic hypoglycemia in IDDM (2,36,37). Third, epinephrine responses to hypoglycemia are reduced little, if at all, in classical diabetic autonomic neuropathy per se (23,36), whereas reduced epinephrine responses are a cardinal feature of hypoglycemia unawareness. Thus, although reduced autonomic responses to a given degree of hypoglycemia, including reduced parasympathetic (pancreatic polypeptide) as well as adrenomedullary (epinephrine) responses, are a central feature of hypoglycemia unawareness, these impairments are not the result of classical diabetic autonomic neuropathy. Therefore, hypoglycemia unawareness exemplifies a different form of diabetic autonomic failure, termed descriptively, hypoglycemia-associated autonomic failure (4,23), which is specific for the stimulus of hypoglycemia.

Hypoglycemia-associated autonomic failure in general, and hypoglycemia unawareness in particular, is probably multifactorial in origin (13). The hypoglycemia-associated clinical syndromes—hypoglycemia unawareness, defective glucose counterregulation, and elevated glycemic thresholds for symptoms and counterregulatory activation during effective intensive therapy—that exemplify hypoglycemia-associated autonomic failure are clinically and, therefore, potentially pathogenetically interrelated. For example, the glycemic thresholds for autonomic symptoms (i.e., awareness of hypoglycemia) are elevated

(lower plasma glucose concentrations are required) in patients with defective glucose counterregulation and in patients with better glycemic control (13), as well as in those with clinical hypoglycemia unawareness. However, the pathogenetic mechanisms of these syndromes are unknown. Although these mechanisms likely are different from that of classical diabetic autonomic neuropathy, they are not necessarily the same in all three syndromes, and might well be multiple in a given syndrome.

It is conceivable that antecedent iatrogenic hypoglycemia, even recent short-term antecedent hypoglycemia, might be one factor, perhaps a major factor, in the pathogenesis of at least one form of hypoglycemia unawareness, and of hypoglycemia-associated autonomic failure in general (4). It is now clear that recent antecedent hypoglycemia results in substantially higher glycemic thresholds (lower glucose levels required) for symptomatic and autonomic responses to subsequent hypoglycemia in nondiabetic humans (38–40). For example, we (38) found that a single 2-h episode of afternoon hypoglycemia reduced the symptomatic and neuroendocrine, including autonomic, responses to hypoglycemia the next morning in nondiabetic humans. To the extent that this phenomenon occurs in patients with IDDM, it leads logically to the following hypothesis: Recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure, and hypoglycemia-associated autonomic failure, by reducing both the symptoms of (awareness of) and defenses against developing hypoglycemia, results in recurrent severe hypoglycemia, thus creating a vicious cycle (4). If this hypothesis is confirmed in patients with IDDM, as recent data suggest (23), it will suggest a relatively straightforward approach to the prevention of hypoglycemia-associated autonomic failure, including at least one form of hypoglycemia unawareness.

How might an episode of hypoglycemia cause a decreased symptomatic and autonomic response to a subsequent episode of hypoglycemia? Among the theoretical possibilities, considerable animal data (41,42) raise the possibility of increased fractional extraction of glucose by the brain (and perhaps other tissues), perhaps mediated by increased available glucose transporters (GLUT-1) in the cerebral microvasculature that constitutes the blood-brain barrier (43). However, these phenomena have not been demonstrated in humans (44). Furthermore, if the mechanism were increased glucose transport into the brain at a given level of hypoglycemia, one would expect that all responses would be reduced at that glucose level. Although there is general agreement that neurogenic symptomatic and autonomic neuroendocrine responses to hypoglycemia are reduced after an episode of antecedent hypoglycemia (38–40), there is less agreement concerning the neuroglycopenic symptomatic and cognitive responses. We (23,38) found neuroglycopenic symptomatic responses to also be reduced, but Widom and Simonson (40) did not. Furthermore, there is disagreement as to whether neuroglycopenic manifestations are (13) or are not (45–47) reduced and whether cognitive function is (48) or is not (47) reduced at a given level of hypoglycemia in intensively treated IDDM, perhaps an example of elevated glycemic thresholds for neurogenic symptoms and autonomic responses attributable to antecedent hypoglycemia.

Another suggestion, based on a clinical observation after the introduction of human insulin but lacking a clear theoretical rationale, is that treatment with human compared with animal insulin may produce relative hypoglycemia unawareness (49–52). In a follow-up of the initial report of Teuscher and Berger (49), Berger et al. (50) conducted a prospective study and found hunger and sweating were less frequent initial symptoms of hypoglycemia, whereas neuroglycopenic symptoms were more frequent initial symptoms of hypoglycemia during treatment with human insulin.

Egger et al. (51) re-examined this issue in a prospective, randomized, double-blind, crossover trial in which 44 people with IDDM used human insulin for 6 wk and porcine insulin for 6 wk. No differences were noted in routinely self-monitored blood-glucose concentrations, glycemic control, or mean daily insulin doses during treatment with the two insulins. The patients completed symptom questionnaires after each episode of hypoglycemia (with glucose levels of ≤2.8 mM determined with a monitor). Analysis of 493 questionnaires (234 hypoglycemic episodes during treatment with human insulin and 259 hypoglycemic episodes during treatment with porcine insulin) disclosed that some symptoms of hypoglycemia were reported more frequently during treatment with human insulin. These symptoms were lack of concentration (53 vs. 35%), restlessness (50 vs. 38%), and confusion (30 vs. 20%). No differences were observed in the frequencies of the symptoms of sweating, tremor, hunger, or visual disturbance during treatment with the two insulins. Analysis of the data per patient rather than per questionnaire confirmed that more patients reported lack of concentration (52 vs. 35%) and restlessness (53 vs. 45%), but not confusion, as symptoms of hypoglycemia during treatment with human insulin; fewer patients reported hunger (33 vs. 42%) during treatment with human insulin. In addition to confusion, the symptoms of sweating, tremor, and visual disturbance were reported by patients in similar proportions during treatment with the two insulins. Thus, the data are internally consistent with respect to the hypoglycemic symptoms of lack of concentration and restlessness, but not those of confusion and hunger. These data support the earlier report (50) in that one clear neuroglycopenic symptom, lack of concentration, was found to be more common during treatment with human insulin. However, they do not support the earlier suggestion (50) that sweating and hunger are less frequent symptoms of hypo-

glycemia during treatment with human insulin. The latter is, of course, fundamentally important because sweating and hunger are important warning symptoms of developing hypoglycemia, as discussed earlier. In addition to the fact that there were fewer documented episodes of hypoglycemia, there were significantly fewer glucose levels of <2.8 mM found on routine self-blood glucose monitoring during treatment with human insulin in the trial (51). There was one episode of hypoglycemic coma during treatment with human insulin, and two such episodes during treatment with porcine insulin. Thus, the data do not indicate, or even suggest, that the observed apparent differences in symptom patterns result in an increased frequency or severity of clinical hypoglycemia during treatment with human compared with porcine insulin.

To address the clinical issue, Egger et al. (52) conducted a retrospective case-control study of 112 hospital (including emergency room only) admissions (of 94 individuals with IDDM) for iatrogenic hypoglycemia. Treatment with human insulin was found to be more frequent in the hypoglycemic cases (46%) than in the nonhypoglycemic control patients (34%). Of the patients using human insulin, 90% had been transferred from animal insulins, most within the year before admission. Thus, treatment with human insulin (as well as a history of hypoglycemic coma and evidence of tight glycemic control) was found to be a risk factor for iatrogenic hypoglycemia that prompts a hospital visit. Potential confounding variables considered, and rejected, by the authors included unidentified risk factors, admission bias, and previous hypoglycemia as a reason for changing to human insulin (52). An additional potential confounding variable is the inclination of patients and/or physicians to attempt to improve glycemic control at the time of initiation of treatment with a new insulin. Finally, the appropriateness of the inclusion of the index patient (who died from hypoglycemia after transfer to human insulin) is open to question, at least in the absence of a statement citing the number of admissions of that patient. Although the data were not presented, the findings were said to be similar when the data were analyzed by patient rather than by admission.

There have been some seemingly supportive reports from other investigative groups. For example, Heine et al. (53), using a hyperinsulinemic-hypoglycemic clamp technique, reported reduced autonomic symptoms and plasma norepinephrine responses to hypoglycemia produced with human insulin in nondiabetic subjects, compared with that produced by porcine insulin. However, Kern et al. (54), using a similar experimental design, did not confirm those findings. On the other hand, in another study, Kern et al. (55) reported stronger auditory evoked potential responses during hypoglycemia produced with porcine compared with human insulin. Finally, Daneman and Zinman (56) noted that they had observed 3 patients who suffered severe hypoglycemia without warning symptoms after transfer from beef-pork to human insulin.

All things considered, however, both the older body of evidence (for review, see 57) and more recent comparative studies of the glucose counterregulatory (54,58–61) and symptomatic (58,60,62) responses to hypoglycemia produced with human and porcine insulin have not provided support for this hypothesis. Notably, one of these studies, reporting no differences in the symptomatic, neuroendocrine, or cognitive responses to hypoglycemia produced by human and porcine insulin was conducted in patients who specifically reported loss of awareness after the change to human insulin, with return of awareness after resumption of treatment with animal insulin (61). Similarly, cross-sectional studies of the frequency of clinical hypoglycemia during treatment of IDDM with human or animal insulin have not disclosed differences (63–65). For example, Muhlhauser et al. (63) questioned 247 patients treated with animal insulins and 276 patients treated with human insulin. The frequencies of sweating (19 vs. 22%, respectively), trembling (19 vs. 17%, respectively) and unrest (15 vs. 11%, respectively) as initial symptoms of hypoglycemia were not different. Similarly, the patients' estimates of their most reliable symptom of hypoglycemia did not differ between the treatment groups. The incidence of severe hypoglycemia, defined as loss of consciousness treated with glucagon or intravenous glucose, did not differ between the animal insulin- and human insulin-treated groups (0.45 vs. 0.46 episodes/patient-yr, respectively). Finally, Colagiuri et al. (66) reported a prospective, randomized, double-blind, crossover comparison of treatment with human and porcine insulin in 50 patients who had previously reported reduced awareness of hypoglycemia after transfer from porcine to human insulin. There were no differences in the frequency of hypoglycemia, or in that of hypoglycemia with reduced or absent awareness during treatment with human or porcine insulin. Thus, there is no compelling support for the hypothesis that treatment with human compared with animal insulin produces clinically important hypoglycemia unawareness in individuals with IDDM.

In short, it appears that the earlier conclusions of Pickup (67) that "if there is an increased risk of unexpected hypoglycaemia on transferring from porcine to human insulin it affects only a few patients. . . ," and of Gale (68) that "there is no evidence that severe hypoglycaemia is more common in patients on human insulin. . . " remain valid.

CONCLUSIONS — Hypoglycemia unawareness, along with the other hypoglycemia-associated clinical syndromes of defective glucose counterregulation and elevated glycemic thresholds for symptoms and activation of glucose counterregulatory systems during effective inten-

sive therapy, is a major risk factor for severe iatrogenic hypoglycemia in IDDM. To achieve and safely maintain near normoglycemia in most people with IDDM, we must learn to deliver insulin in a much more physiological fashion, or learn to prevent, correct or compensate for these forms of hypoglycemia-associated autonomic failure in IDDM. Pending such advances, application of the principles of current insulin therapy, including patient education, self-monitoring of blood glucose, and professional support, must be coupled with prudent glycemic goals to minimize the frequency of severe hypoglycemia without completely compromising metabolic control.

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Note Added in Proof: Prospective data indicating a 7-fold higher frequency of severe iatrogenic hypoglycemia in patients with reduced awareness of hypoglycemia have been presented: MacLeod KM, Gold AE, Frier BM: Frequency of severe trypoglycemia in insulin-dependent diabetic patients with altered awareness of hypoglycemia (Abstract). *Diabetes* 42:26A, 1993.

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