

Hypoglycemia Begets Hypoglycemia in IDDM

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Iatrogenic hypoglycemia causes recurrent physical morbidity, and some mortality, as well as recurrent or persistent psychological morbidity in patients with IDDM (1). The frequency of iatrogenic hypoglycemia is substantially higher during effective intensive therapy of IDDM. Even in the highly structured Diabetes Control and Complications Trial the frequency of severe hypoglycemia was increased more than threefold in intensively treated IDDM (2). Given the demonstration that effective intensive therapy makes a difference (it reduced the development and progression of retinopathy, nephropathy, and neuropathy in the Diabetes Control and Complications Trial [2]), and assuming that this finding will lead to more widespread attempts to keep plasma glucose concentrations as close to the nondiabetic range as possible, iatrogenic hypoglycemia will almost assuredly become an even greater problem for patients with IDDM.

Because current insulin replacement regimens are far from perfect, absolute or relative insulin excess must occur from time to time in IDDM. This occurs, for example, when insulin doses are excessive or ill-timed, after missed meals or snacks, during an overnight fast, and during or after unusual physical activity. However, it has become increasingly clear that the risk of iatrogenic hypoglycemia is not determined by insulin excess alone but rather by the interplay of insulin excess and compromised glucose counterregulation (1).

Recognized syndromes of compromised glucose counterregulation in IDDM include defective glucose counterregulation (3,4), hypoglycemia unawareness (5, 6), and effective intensive therapy per se (7). These are associated with a high frequency of iatrogenic hypoglycemia, segregate together clinically, and share several pathophysiological features including elevated glycemic thresholds (lower plasma glucose levels required) for autonomic activation and symptoms. Therefore, we have conceptualized them as examples of hypoglycemia-associated autonomic failure (8).

The finding that a single <2-h episode of afternoon hypoglycemia caused reduced autonomic and symptomatic responses to hypoglycemia the following morning in nondiabetic humans (9), coupled with conceptually similar data from other laboratories (10,11), led us to suspect that recent antecedent hypoglycemia might be one cause of hypoglycemia-associated autonomic failure in IDDM. Our overall hypothesis is that in patients with IDDM, recent antecedent iatrogenic hypoglycemia is a major cause of hypoglycemia-associated autonomic failure and the latter, by reducing both symptoms of and physiological defense against developing hypoglycemia, results in recurrent iatrogenic hypoglycemia, thus creating a vicious cycle (8). Two key elements of this hypothesis have been confirmed. In patients with IDDM, a single <2-h episode of afternoon hypoglycemia causes both elevated glycemic thresholds for autonomic activation and symptoms and lower nadir plasma glucose concentrations during moderate hyperinsulinemia the following morning (12).

The finding of reduced autonomic and symptomatic (both neurogenic and neuroglycopenic) responses and lesser impairment of cognitive function at a given level of hypoglycemia (i.e., elevated glycemic thresholds for all of these) in patients with insulinomas, and reversal of these abnormalities after surgical removal of the tumors, provides indirect support for the concept that recent antecedent hypoglycemia might lead to recurrent iatro-

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IDDM, insulin-dependent diabetes mellitus.

genic hypoglycemia in IDDM (13). Furthermore, the fact that experimental asymptomatic nocturnal hypoglycemia produces a similar pattern (14) is worrisome from a clinical perspective because iatrogenic hypoglycemia often occurs during the night and is not recognized.

A long-recognized clinical syndrome in IDDM (5), hypoglycemia unawareness, is loss of the neurogenic (autonomic) warning symptoms that previously allowed the patient to recognize developing hypoglycemia (15) and take action (e.g., eat) to prevent its progression to severe neuroglycopenia. Recently presented prospective data indicate that a clinical history of hypoglycemia unawareness is associated with a fivefold increased frequency of severe iatrogenic hypoglycemia (6).

To what extent is recent antecedent iatrogenic hypoglycemia involved in the pathogenesis of hypoglycemia unawareness, as suggested by the hypoglycemia-associated autonomic failure hypothesis, in the clinical setting of intensive therapy of IDDM? In the November issue of *Diabetes*, Fanelli et al. (16) reported their approach to this question. They studied 8 intensively treated patients with a relatively short duration of IDDM (≤ 7 yr) and a history of hypoglycemia unawareness before, after 2 wk, and after 3 mo of vigorous attempts to avoid iatrogenic hypoglycemia. The latter resulted in a decreased frequency of detected hypoglycemia and an increase in mean HbA_{1c} (from 5.8 to 6.9%). Compared with nondiabetic individuals, autonomic and symptomatic responses and cognitive dysfunction at a given level of hypoglycemia were reduced initially in the patients. These improved after 2 wk, and more so after 3 mo of attempts to avoid iatrogenic hypoglycemia. Indeed, at 3 mo, symptomatic (neurogenic and neuroglycopenic), cognitive, and plasma pancreatic polypeptide (as well as growth hormone and cortisol) responses to hypoglycemia were indistinguishable from those of nondiabetic subjects. Plasma epinephrine, and even glucagon, responses were increased albeit not normalized. These investigators have recently presented generally similar findings at 1 yr of follow-up (17).

Fanelli et al. (16) expressed concern that the observed changes might be less marked in patients with a longer duration of IDDM, and that greater deterioration of glycemic control might occur over time. To some extent, these concerns appear to be supported by their longer experience (17). Although one might point out the absence of a control group of patients who continued their previous regimens without attempts to avoid iatrogenic hypoglycemia in the original study (16), it is unlikely that the abnormal responses documented at baseline would have reverted to normal in such a group (17). It is perhaps conceivable that some aspect of the changes in management other than a reduced frequency of iatrogenic hypoglycemia was responsible, but that seems unlikely. Similarly, it is conceivable, but again unlikely, that the reduced frequency of iatrogenic hypoglycemia was the result of higher glycemic goals alone rather than increased symptomatic and counterregulatory hormone (particularly epinephrine) responses to developing hypoglycemia in the setting of higher glycemic goals.

Thus, it appears that the frequency of iatrogenic hypo-

glycemia can be reduced by relatively short-term scrupulous avoidance of iatrogenic hypoglycemia (8). Although they obviously need to be confirmed independently, the data of Fanelli et al. (16) provide strong evidence that the syndrome of hypoglycemia unawareness is largely reversible. The data are less clear-cut with respect to the syndrome of defective glucose counterregulation. The observed enhanced epinephrine responses would be expected to be physiologically important (1,3,4). The observed increased glucagon responses raise the possibility that defective glucose counterregulation might also be reversible, but the increases were small and the glucagon responses were still substantially deficient. Obviously, this potentially very important observation needs to be confirmed. Finally, it is likely that the elevated glycemic thresholds for autonomic activation and symptoms that occur during effective intensive therapy (7) are the result of recent antecedent hypoglycemia (18). Similarly, the reduced thresholds found in poorly controlled IDDM (19) may be the result of the absence of recent antecedent hypoglycemia.

Clearly, many important questions remain unanswered. At a basic level, what is the mechanism(s) of the elevated glycemic thresholds induced by recent hypoglycemia? At a clinical level, what strategies will permit application of this insight to the management of IDDM without compromising glycemic control? Progress in the understanding of the physiology of glucose counterregulation and its pathophysiology in IDDM, and the relationship of the latter to clinical iatrogenic hypoglycemia, has been substantial. However, the goal of eliminating hypoglycemia from the lives of patients with IDDM without compromising glycemic control remains elusive. Documentation of the fact that glycemic control makes a difference (2) makes it even more imperative that this goal be achieved.

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