

# Attenuated Sympathoadrenal Responses, but Not Severe Hypoglycemia, During Aggressive Glycemic Therapy of Early Type 2 Diabetes

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Iatrogenic hypoglycemia is a major limiting factor in the strict glycemic management of diabetes (1,2). Hypoglycemia can cause recurrent morbidity in many people with type 1 diabetes and also in some with advanced type 2 diabetes (2,3). Rarely fatal, fear of hypoglycemia precludes maintenance of euglycemia over a lifetime with diabetes and full realization of the vascular benefits of glycemic control. Hypoglycemic events compromise defenses against subsequent falling plasma glucose concentrations and thus cause a vicious cycle of recurrent hypoglycemia.

Hypoglycemia in diabetes is fundamentally the result of episodes of therapeutic hyperinsulinemia caused by treatment with an insulin secretagogue or insulin. In general, the incidence of iatrogenic hypoglycemia is a function of the degree of  $\beta$ -cell failure (1,2,4), and risk is predicted by the absence of evidence of endogenous insulin secretion (C-peptide) (5). Incidence of hypoglycemia is lower in people with type 2 diabetes, who are not usually completely insulin deficient, than in those with type 1 diabetes, and this is especially true early in the course of type 2 diabetes. However, the incidence of hypoglycemia increases progressively over time (6), ultimately approximating that in those with type 1 diabetes (7,8), as type 2 diabetic individuals approach the insulin-deficient end of the spectrum. Because type 2 diabetes is  $\sim$ 20-fold more prevalent than type 1 diabetes and many people with type 2 diabetes ultimately require treatment with insulin, most episodes of iatrogenic hypoglycemia, including severe hypoglycemia, occur in those with type 2 diabetes (1–3,9).

The key physiological defenses against falling plasma glucose concentrations are 1) a decrease in insulin secretion; 2) an increase in glucagon secretion; and, in the absence of the latter, 3) an increase in epinephrine secretion (1,2). The behavioral defense is carbohydrate ingestion prompted by perception of the largely sympathetic neural neurogenic symptoms that cause the individual to become aware of hypoglycemia (10,11). Although these mechanisms are intact early in the course of type 2

diabetes when endogenous insulin deficiency is only relative, the insulin and glucagon responses are typically compromised in people with absolute endogenous insulin deficiency in type 1 diabetes (1,2,12) and in those with advanced type 2 diabetes (13). Epinephrine, sympathetic nervous system, and symptomatic responses are further compromised in a subset of patients, causing, in large part, the clinical syndrome of hypoglycemia unawareness with a greatly increased risk of severe hypoglycemic episodes (14). Because experimentally induced recent antecedent hypoglycemia (as well as exercise and the state of deep sleep) produces defective epinephrine, sympathetic neural, and symptom responses to subsequent hypoglycemia (15,16) and to underscore the key role of the attenuated sympathoadrenal responses in defense against severe hypoglycemia, this pathophysiology has been termed hypoglycemia-associated autonomic failure (HAAF) in diabetes (1,2,13). The attenuated epinephrine secretory response causes defective glucose counterregulation in the setting of absolute  $\beta$ -cell failure. The concept of HAAF was developed in the context of type 1 diabetes (1,2), and its role in the pathogenesis of hypoglycemia in type 2 diabetes (1,2,9) remains to be clarified.

As reported in this issue of *Diabetes*, Davis et al. (17) address this issue, studying 15 patients with relatively early type 2 diabetes. Mean duration of known diabetes was only 6 years. At baseline patients had no evidence of compromised physiological or behavioral defenses against hypoglycemia. Even after overnight insulin infusions to maintain near euglycemia, mean fasting plasma C-peptide concentrations were higher than those of patients with type 1 diabetes (18,19). Importantly, insulin secretion as assessed by C-peptide levels fell appropriately, by  $\sim$ 75%, when plasma glucose concentrations were lowered to 3.3 mmol/l (60 mg/dl), just below the postabsorptive physiological range of  $\sim$ 3.9–6.1 mmol/l (70–110 mg/dl). At a plasma glucose concentration of 3.3 mmol/l (60 mg/dl), increments in plasma glucagon and epinephrine were similar to those of nondiabetic control patients, and muscle sympathetic nerve activity (MSNA) and symptomatic responses were enhanced. Perhaps this reflects the experience of hyperglycemia, as the mean A1C was just over 10%, indicating very poor glycemic control. Exaggerated counterregulatory response to hypoglycemia in those with type 2 diabetes has been described previously (20).

In the patients with poor glycemic control in Davis et al.'s study, two episodes of subphysiological plasma glucose concentrations reduced an array of responses (including glucagon and epinephrine, MSNA, and symptoms) to hypoglycemia the following day (17). This has been well documented in nondiabetic subjects and those with type 1 and type 2 diabetes (1,2,12). However, it is of interest that

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this was demonstrated following low plasma glucose levels as high as 3.3 mmol/l (60 mg/dl) (17).

The novelty of the Davis et al. study is that, following the first hypoglycemia investigation, patients were brought into strict glycemic control with intensification of lifestyle and oral agent therapy, reducing mean A1C levels to 6.7% in 6 months with, remarkably, no overall weight gain. Treatment was associated with an increase in self-reported glucose levels <3.9 mmol/l (70 mg/dl) from 1.1 to 3.2 per patient per month on intensive home monitoring, although only four patients reported glucose levels <2.8 mmol/l (50 mg/dl). Unfortunately, the extent to which any of these were symptomatic was not reported, and it is not clear that the self-monitoring was as intensive before the intensification of therapy. There were no episodes of major hypoglycemia. This change in glycemic experience was associated with a substantial reduction in the plasma epinephrine, MSNA, and symptomatic responses to plasma glucose concentrations of 3.3 mmol/l (60 mg/dl) (~50, 66, and 40%, respectively), a novel finding in early type 2 diabetes, although it has been shown in advanced type 2 diabetes that required insulin to improve control (21). Notably, in the Davis et al. study, decrements in insulin secretion and increments in glucagon secretion were not reduced, and only the epinephrine responses were reduced significantly compared with those of healthy control subjects.

Coupled with reports of other investigators cited by Davis et al. (17), these data provide further insight into the pathophysiology of glucose counterregulation in diabetes by the application of state-of-the-art assessment methods in a clinically relevant setting. The data provide both further documentation that sympathoadrenal and symptomatic responses to hypoglycemia are exaggerated in early type 2 diabetic patients with poor glycemic control and new evidence that aggressive glycaemic therapy in these patients results in attenuation of responses to subsequent low plasma glucose concentrations (17). This effect is most plausibly attributed to reduced exposure to hyperglycemia and an increased frequency of subphysiological glucose levels during intensive therapy. Further, immediately antecedent iatrogenic hypoglycemia causes a further reduction in the vigor of the counterregulatory responses.

Are there clinical implications from these data? Hypoglycemia sufficient to cause cognitive impairment (not measured by Davis et al.) can diminish quality of life. Functional sympathoadrenal failure might be relevant to the pathogenesis of rare, but potentially fatal, ventricular arrhythmias (22). Concern has arisen about the possible involvement of hypoglycemia in the adverse effects of rapid intensification of diabetes therapies in late and complicated type 2 diabetes (23,24). In the present study, it is noteworthy that in patients with relatively early type 2 diabetes the changes seen in the responses to experimentally induced hypoglycemia were not associated with an increased frequency of major clinical hypoglycemia, perhaps because  $\beta$ -cell failure was not sufficient to cause loss of the insulin and glucagon responses (1,2). Data from follow-up studies show the prolonged benefit of early intensive glucose management in preventing vascular complications of diabetes (25,26). These data, taken in context with other published work showing possible problems of taking action much later in the course of the disease, would seem to be a further encouragement

to implementing good control of diabetes as early as possible.

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