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

Stephanie A. Amiel[1] and Philip E. Cryer[2]

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 β-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 ~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 β-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 ~75%, when plasma glucose concentrations were lowered to 3.3 mmol/l (60 mg/dl), just below the postabsorptive physiological range of ~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

From the [1]Department of Medicine, King's College London School of Medicine, London, U.K.; and the [2]Division of Endocrinology, Metabolism and Lipid Research, Washington University School of Medicine, St. Louis, Missouri.

Corresponding author: Stephanie A. Amiel, stephanie.amiel@kcl.ac.uk.

DOI: 10.2337/db08-1647

See accompanying original article, p. 701.

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 glycemic 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 β-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.

ACKNOWLEDGMENTS

The original cited work of P.E.C. has been supported, in part, by U.S. Public Health Service National Institutes of Health grants R37 DK27085, MO1 RR00036 (now UL1 RR24992), and P60 DK20579 and by a fellowship award from the American Diabetes Association.

P.E.C. has served as a consultant to MannKind, Marcadia Biotech, Medtronic MiniMed, and Merck in the past year. S.A.A. has served on advisory boards for Medtronic Minimed, Amylin Europe, Eli Lilly U.K., NovoNordisk, Novartis, and Merck Sharp and Dohme. No other potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Cryer PE: The barrier of hypoglycemia in diabetes. *Diabetes* 57:3169–3167, 2008
2. Cryer PE: *Hypoglycemia in Diabetes: Pathophysiology Prevalence and Prevention.* Alexandria, VA, American Diabetes Association, 2009
3. Zammitt NN, Frier BM: Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 28:2948–2961, 2005
4. Donnelly LA, Morris AD, Frier BM, Ellis JD, Donnan PT, Durrant R, Band MM, Reekie G, Leese GP, The DARTS/MEMO Collaboration: Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 22:749–755, 2005
5. Mühlhauser I, Overmann H, Bender R, Bott U, Berger M: Risk factors for severe hypoglycaemia in adult patients with type 1 diabetes: a prospective population-based study. *Diabetologia* 41:1274–1282, 1998
6. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
7. Leese GP, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, Frier BM, Morris AD, DARTS/MEMO Collaboration: Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 26:1176–1180, 2003
8. U.K. Hypoglycaemia Study Group: Risk of hypoglycaemia in type 1 and 2 diabetes: effects of treatment modalities and their duration. *Diabetologia* 50:1140–1147, 2007
9. Amiel SA, Dixon TD, Mann R, Jameson K: Hypoglycaemia in type 2 diabetes. *Diabet Med* 25:245–254, 2008
10. Towler DA, Havlin CE, Craft S, Cryer PE: Mechanism of awareness of hypoglycemia: perception of neurogenic (predominantly cholinergic) rather than neuroglycopenic symptoms. *Diabetes* 42:1791–1798, 1993
11. DeRosa MA, Cryer PE: Hypoglycemia and the sympathoadrenal system: neurogenic symptoms are largely the result of sympathetic neural, rather than adrenomedullary, activation. *Am J Physiol Endocrinol Metab* 287: E32–E41, 2004
12. Dagogo-Jack SE, Craft S, Cryer PE: Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. *J Clin Invest* 91:819–828, 1993
13. Segel SA, Paramore DS, Cryer PE: Hypoglycemia-associated autonomic failure in advanced type 2 diabetes. *Diabetes* 51:724–733, 2002
14. Ryder RE, Owens DR, Hayes TM, Ghatei MA, Bloom SR: Unawareness of hypoglycaemia and inadequate hypoglycaemic counterregulation: no causal relation with diabetic autonomic neuropathy. *BMJ* 301:783–787, 1990
15. Heller S, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. *Diabetes* 40:223–226, 1991
16. Davis SN, Shavers C, Mosqueda-Garcia R, Costa F: Effects of differing antecedent hypoglycemia on subsequent counterregulation in normal humans. *Diabetes* 46:1328–1335, 1997
17. Davis SN, Mann S, Briscoe VJ, Ertl AC, Tate DB: Effects of intensive therapy and antecedent hypoglycemia on counterregulatory responses to hypoglycemia in type 2 diabetes. *Diabetes* 58:701–709, 2009
18. Gjessing HJ, Matzen LE, Faber OK, Frølund A: Fasting plasma C-peptide, glucagon stimulated plasma C-peptide, and urinary C-peptide in relation to clinical type of diabetes. *Diabetologia* 32:305–311, 1989

19. Service FJ, Rizza RA, Zimmerman BR, Dyck PJ, O'Brien PC, Melton LJ III: The classification of diabetes by clinical and C-peptide criteria: a prospective population-based study. *Diabetes Care* 20:198–201, 1997
20. Spyer G, Hattersely AT, Macdonald IA, Amiel SA, MacLeod KM: Hypoglycaemic counterregulation at "normal" blood glucose concentrations in patients with well-controlled type 2 diabetes. *Lancet* 356:1970–1974, 2000
21. Korzon-Burakowska A, Hopkins D, Matyka K, Lomas J, Pernet A, Macdonald IA, Amiel SA: Effects of glycemic control on protective responses against hypoglycemia in type 2 diabetes. *Diabetes Care* 21:282–290, 1998
22. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R: Antecedent hypoglycemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. *Diabetes* 58:360–366, 2009
23. Robinson RT, Harris ND, Ireland RH, Macdonald IA, Heller SR: Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with type 1 diabetes. *Diabetologia* 47:312–315, 2004
24. Dluhy RG, McMahon GT: Intensive glycemic control in the ACCORD and ADVANCE trials. *N Engl J Med* 358:2630–2633, 2008
25. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group: Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 353:2643–2653, 2005
26. Holman RR, Paul SK, Ethel MA, Matthews DR, Neil HAW: 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 359:1577–1589, 2008