Psychobehavioral Metabolic Parameters of Severe Hypoglycemic Episodes

Investigators have discussed the incidence of severe hypoglycemia (1,2) and its consequences in terms of skeletal muscle damage (3) and both transient (4) and long-term (5) cognitive impairments. We (6) and others (7,8) have presented retrospective data that indicate the aversive consequences and subsequent fear of hypoglycemia that may promote a phobia toward hypoglycemia and in turn prompt avoidance behaviors that attempt to maintain elevated blood glucose (BG) to avoid future hypoglycemia. Trauma-fear-avoidance behavior can then be responsible for significant metabolic disruption. This case report presents prospective data that illustrate this phenomenon and suggests additional concerns associated with hypoglycemia and a new focus of intervention.

A 37-yr-old 210-lb large-frame White married male realtor of above-average intelligence participated in a study investigating the therapeutic effects of continuous subcutaneous insulin infusion (CSII) therapy. The protocol for this study involved counterregulation testing before and after CSII and psychological testing including the Hypoglycemic Fear Survey (6–8). On 22 September 1988, the patient was admitted to the Clinical Research Center, and at 2200, he was placed on overnight variable intravenous infusion of human regular insulin to sustain euglycemia. At 0900 the next morning, a standard 120-min continuous infusion of human regular insulin (0.67 mU · kg^{-1} · min^{-1}) was begun to determine ability to counterregulate (9). The patient's BG counterregulated at 50 mg/dl 60 min into the protocol. Epinephrine rose from 240 to 1090 pg/dl between 40 and 60 min, and pancreatic polypeptide similarly rose from 55 to 740 pg/dl. These data clearly indicate that the patient counterregulated to hypoglycemia.

Four months later (15 January 1989), the patient was hospitalized to be trained and placed on CSII with a basal insulin rate of 0.7 U · kg^{-1} · day^{-1}. He returned monthly for follow-up and glycosylated hemoglobin (HbA_1) determinations. After 3 mo of CSII (25 March 1989), he unexpectedly learned that his wife was pregnant and subsequently had several low (<70 mg/dl) self-monitoring of blood glucose readings throughout the day. Despite a BG of 50 mg/dl at bedtime, he failed to reduce his basal insulin rate. At ~0400, he experienced a severe hypoglycemic seizure, during which he shattered his left clavicle, which required reconstructive surgery. His BG level was recorded as 2 mg/dl in the emergency room. A subsequent computerized axial tomography scan was negative. Total medical expenses resulting from this hypoglycemic episode were $22,000. The patient returned to work 3 days postseizure.

The first four HbA_1 readings before this seizure were 10.5, 11.8, 11.4, and 9.8. Eight, 12, and 18 wk after the seizure, HbA_1 rose to 13.8, 14.9, and 13.8, respectively. His score on the worry scale of the Hypoglycemic Fear Survey (6–8), a scale that quantifies to what extent a patient is preoccupied with concerns about hypoglycemia, rose by nearly 40% after his hypoglycemic experience, compared with his three previous scores (worry scale = 23, 26, 24 for 3 mo before seizure, and 36 after seizure). Item analysis of the worry scale indicated increased concern over *1*) having a hypoglycemic episode while asleep, *2*) having a seizure, and *3*) losing control.

During an interview 3 mo after the seizure, the patient reported that he had been extremely frightened by the hypoglycemic seizure. Because of the fear that a similar episode would recur, he attempted to maintain his BG in a "safer" and higher range than previously. The patient said he thought that he "needed a little padding" in case his BG fell again. The patient also noted that his HbA_1 measurements had been affected by these changes in his self-treatment and reported trying very hard to return to his previous pattern of intensive treatment. Additionally, he reported that his wife was even more intimidated by the hypoglycemic episode than he was, and she encouraged him to maintain elevated BGs. A counterregulation test repeated at this time (22 June 1989) demonstrated that the patient's BG again counterregulated 80 min into the insulin infusion at 40 mg/dl, in which epinephrine rose from 71 to 471 pg/dl between 60 and 80 min, and pancreatic polypeptide similarly rose from 40 to 980 pg/dl.

This case study illustrates that, although the ability to counterregulate during standardized insulin infusion protocols is associated with reduced risk of severe hypoglycemia (9), the ability to counterregulate does not preclude severe hypoglycemic episodes. Secondly, although the acute physical and cognitive effects may resolve quickly, the psychobehavioral effects of severe hypoglycemia may linger for a long period and possibly contribute to continued metabolic dysregulation. Clinicians should routinely look for such psychological sequelae to hypoglycemia and its behavioral metabolic consequences, possibly with the Hypoglycemic Fear Survey. Subsequent efforts to reestablish metabolic control should then focus on eliminating this psychological barrier to appropriate self-care behaviors and readjusting the insulin-diet regimen.

From the Department of Behavioral Medicine and Psychiatry, University of Virginia Health Sciences Center, Charlottesville, Virginia; and Washington University, St. Louis, Missouri.

Address correspondence and reprint requests to Dr. Daniel J. Cox, Department of Behavioral Medicine and Psychiatry, Drawer F, Building 915, Blue Ridge Hospital, Charlottesville, VA 22901.

ACKNOWLEDGMENTS

This research was supported by National Institutes of Health Grants DK-28288 and RR-00847 and a grant from Eli Lilly and Company.

DANIEL J. COX, PhD
LINDA GONDER-FREDERICK, PhD
BASIM ANTOUN, MD
WILLIAM CLARKE, MD
PHILIP CRYER, MD

REFERENCES

1. Lorenz R, Siebert C, Cleary P, Santiago J, Heyse S, for the DCCT Research Group: Epidemiology of severe hypoglycemia in the DCCT (Abstract). *Diabetes* 37 (Suppl. 1):3A, 1988
2. The DCCT Research Group: Diabetes Control and Complications Trial (DCCT): results of feasibility study. *Diabetes Care* 10:1–19, 1987
3. Hepburn DA, Steel JM, Frier BM: Hypoglycemic convulsions cause serious musculoskeletal injuries in patients with IDDM. *Diabetes Care* 12:32–34, 1989
4. Holmes CS, Hayford JT, Gonzalez JL, Weydert JA: A survey of cognitive functioning at different glucose levels in diabetic persons. *Diabetes Care* 6:180–85, 1983
5. Wredling R, Lins PE, Adamson U, Theorell T, Levander S: Neuropsychological function and personality trait in insulin-dependent diabetic patients with recurrent severe hypoglycemia. *Diabetes Res Clin Pract* 5 (Suppl. 1):5625, 1988
6. Cox DJ, Irvine A, Gonder-Frederick L, Nowacek G, Butterfield J: Fear of hypoglycemia: quantification, validation, and utilization. *Diabetes Care* 10:617–21, 1987
7. Irvine A, Saunders T: Fear of hypoglycemia: replication and validation (Abstract). *Diabetes* 38 (Suppl. 2):109A, 1989
8. Green LB, Wysocki T, Reineck BM: Validation of the hypoglycemic fear survey with children and adolescents (Abstract). *Diabetes* 38 (Suppl. 2):109A, 1989
9. Cryer P, White N, Santiago J: The relevance of glucose counterregulatory systems to patients with insulin dependent diabetes mellitus. *Endocr Rev* 7:131–39, 1986

Insulin Response to Arginine in Puberty

The intravenous glucose tolerance test (IVGTT) has been used to identify subjects with early abnormalities of β-cell function (1). The insulin response to nonglucose stimulus has also been studied in early phases of insulin-dependent diabetes mellitus (IDDM) (2). A graded loss of insulin response to intravenously administered glucose, oral glucose, tolbutamide, and arginine has been described before the onset of IDDM, and the ability of the pancreas to secrete insulin after arginine has been suggested as one possible approach to the assessment of residual β-cell mass during the prediabetic period (2).

Pubertal development is associated with an increase of basal and glucose-stimulated insulin (3–5), which should be considered when analyzing β-cell function in pubertal pre-IDDM subjects. Nevertheless, the response of β-cells to nonglucose stimulus has not been analyzed in pubertal subjects. We studied insulin response to arginine in a group of first-degree relatives of IDDM patients and found that insulin response was increased in pubertal relatives.

We studied 20 subjects (12 islet cell antibody–positive [ICA^+] and 8 ICA^-) from a previously described population of first-degree relatives of IDDM patients (6). Overweight relatives (body mass index [BMI] >26 mg/kg^2) and relatives with a decreased first-phase insulin response to IVGTT were not included in the study. Informed consent was obtained from subjects. An arginine test (0.5 g of 10% arginine monochlorhydrate solution/kg body wt i.v. infused over 30 min; maximum dose 30 g) was performed, and samples for glucose, insulin, and glucagon determination were taken at 0, 5, 10, 20, 30, 40, 50, and 60 min. Blood glucose was determined by a glucose oxidase method adapted to an autoanalyzer. Insulin and glucagon were determined by radioimmunoassay. The coefficients of variation (C.V.s) of the insulin assay were 6.2% (intra-assay) and 6.8% (inter-assay); sensibility was 18 pM. The C.V.s of the glucagon assay were 5.8% (intra-assay) and 6.3% (inter-assay); sensibility was 14.5 ng/L. Results are expressed as means ± SE. Comparisons between groups were tested for significance with the Mann-Whitney test.

Subjects were divided into two groups according to age: group 1, pubertal relatives (12–17 yr old, n = 7); group 2, adult relatives (>17 yr old, n = 13). Clinical and immunological characteristics of both groups are shown in Table 1. Insulin response to arginine was significantly increased in the pubertal group, and no differences were found between pubertal and adult relatives when glucose and glucagon were analyzed (Table 1). Adult relatives were subdivided into groups of young adults (21–29 yr old, n = 5) and adults >30 yr old (n = 8), but no differences were found when basal insulin (59.0 ± 12.0 vs. 72.1 ± 3.8 pM), peak insulin (370 ± 59 vs. 350 ± 34 pM), and insulin area (12,937 ± 2536 vs. 14,007 ± 1697 pM/min) were compared. There were no differences between men and women or between ICA^+ and ICA^- relatives when glucose, insulin, and glucagon (both basal and stimulated) were compared.

TABLE 1
Characteristics of subjects and insulin response to arginine

	<17 yr old	>17 yr old
Age (yr)	15.0 ± 0.6 (12–17)	38.0 ± 3.9 (21–57)
n (M/F)	2/5	8/5
BMI*	20.7 ± 0.7	23.1 ± 0.6
ICA^+/ICA^- (n)	5/2	7/6
Glucose area (mM/min)	354 ± 16	352 ± 23
Fasting insulin (pM)	83.1 ± 8.2	65.6 ± 5.8
Peak insulin (pM)†	579 ± 85	358 ± 32
Insulin area (pM/min)†	23,154 ± 3466	13,561 ± 1520
Glucagon area ($ng \cdot L^{-1} \cdot min^{-1}$)	9874 ± 1447	9759 ± 1004
Ratio of insulin to glucose areas (pM/mM)‡	69.1 ± 7.8	38.2 ± 5.9
Ratio of insulin to glucagon areas (pM/ng)†	2.6 ± 0.5	1.4 ± 0.2

Values are means ± SE. Ranges are in parentheses.
*$P < 0.05$; †$P < 0.02$; ‡$P < 0.01$.