REFERENCES

1. Levitsky LL, Scanu AM, Gould SH: Lipoprotein(a) levels in black and white children and adolescents with IDDM. *Diabetes Care* 14:283–87, 1991
2. Fless GM, Pfaffinger DJ, Eisenbarth JD, Scanu AM: Solubility, immunochemical, and lipoprotein binding properties of apo B-100–apo(a), the protein moiety of lipoprotein(a). *J Lipid Res* 31:909–18, 1990
3. Friedewald WT, Levy RI, Frederickson DS: Estimation of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
4. Massé J: Changes in lipoproteins during weight loss (Letter). *N Engl J Med* 320:668, 1989
5. Massé J: Clinical chemistry reference intervals for healthy elderly subjects (Letter). *Am J Clin Nutr* 51:1115, 1990
6. Massé J: Portable cholesterol analyzers (Letter). *JAMA* 264:1101, 1990
7. Massé J: Effects of diet on serum lipids and apolipoproteins (Letter). *Am J Clin Nutr* 52:765, 1990
8. Massé J: Coffee consumption and serum lipids (Letter). *Am J Med* 89:836, 1990
9. Massé J: LDL-cholesterol equations and SI units (Letter). *Am J Clin Nutr* 53:983, 1991

Reply

As Dr. Massé pointed out in his other letters on this matter (1–6), workers in the United States are prone to make post hoc mass conversions to mM after lipids are calculated in mg/dl. This is indeed the case in our studies; therefore there is no error in our low-density lipoprotein (LDL) values. Our LDL values differ from his predicted values because group means cannot be interpreted in this manner. In addition, a correction has been made for the lipoprotein(a) content of the LDL particle to give a more accurate estimated LDL cholesterol value.

LYNNE L. LEVITSKY, MD
ANGELO M. SCANU, MD
SAMUEL H. GOULD, MD

From the Departments of Pediatrics and Medicine and Biochemistry and Molecular Biology, Pritzker School of Medicine, University of Chicago, Chicago, Illinois.

Address correspondence to Lynne L. Levitsky, MD, Pediatric Endocrine Unit, Massachusetts General Hospital, 709 Wang ACC, 15 Parkman Street, Boston, MA 02114.

REFERENCES

1. Massé J: Changes in lipoproteins during weight loss (Letter). *N Engl J Med* 320:668, 1989
2. Massé J: Clinical chemistry reference intervals for healthy elderly subjects (Letter). *Am J Clin Nutr* 51:1115, 1990
3. Massé J: Portable cholesterol analyzers (Letter). *JAMA* 264:1101, 1990
4. Massé J: Effects of diet on serum lipids and apolipoproteins (Letter). *Am J Clin Nutr* 52:765, 1990
5. Massé J: Coffee consumption and serum lipids (Letter). *Am J Med* 89:836, 1990
6. Massé J: LDL-cholesterol equations and SI units (Letter). *Am J Clin Nutr* 53:983, 1991

Successful Treatment of Unusual Case of Brittle Diabetes With Sulfated Beef Insulin

Brittle diabetes has been defined as episodes of hypoglycemia or hyperglycemia that, whatever their cause, constantly disrupt a patient's life (1). Recognizable causes (1,2) of brittle diabetes are *1*) errors in management by either the patient or medical personnel (including overinsulinization), *2*) intercurrent illnesses, *3*) psychological problems, and *4*) factors influencing the dynamics of insulin action. Although the latter includes insulin-binding antibodies, they have previously been implicated to cause brittle diabetes either by very high titers of insulin-binding antibodies leading to marked hyperglycemia (not hypoglycemia) and clinical insulin resistance (requirement of >200 U insulin/day) (2) or their inability to buffer the egress of subcutaneously injected insulin into the blood stream (3). This report describes a woman on conventional doses of insulin in whom high titers of insulin-binding antibodies caused brittle diabetes (both hypoglycemia and hyperglycemia). Her brittle diabetes was successfully treated by substituting sulfated beef insulin.

A 25-yr-old female insulin-dependent (type I) diabetic patient with diabetes since age 1.5 yr was referred for help with erratic control of her diabetes. Although taking beef ultralente (10 U twice a day) and beef or pork regular insulin before each meal, the patient experienced erratic swings in her blood glucose measured by self-monitoring of blood glucose ≥4 times/day. Many glucose values would be >17 mM regardless of the time of eating or insulin administration. Alternatively, the patient experienced frequent (almost daily) episodes of hypoglycemia, either during the day many hours after taking insulin and/or in the middle of the night. Various human, pork, or beef (both standard and purified) insulin preparations did not seem to help either of these problems.

When first observed, the patient was taking 22 U beef ultralente insulin and 10 U human regular insulin before supper. She ate only at supper to avoid hypoglycemia that occurred at varying unpredictable times during the day if she took regular insulin in the morning. On this regimen, her blood glucose levels usually ranged near 17 mM on awakening and gradually fell during the day. However, she had lost 22 lb, felt generally tired and depressed, and if she ate during the day, would often experience nausea associated with marked hyperglycemia. This approach limited her hypoglycemic episodes to several times a week, occurring mostly in the early overnight hours.

Workup revealed elevated insulin-binding antibodies at 18.5 mU/ml (values >10 mU/ml are assocated with clinical insulin resistance) and a delayed peak response to human insulin given either subcutaneously (9 h) or intravenously (105 min). She was started on sulfated beef regular insulin before each meal and continued to take 22 U beef ultralente insulin before supper.

During the next 10 mo on this regimen, her blood glucose improved (approximately half above and half below 11 mM). She regained 15 lb. Because her antibody values remained elevated (13 mU/ml), she was started on an insulin pump with sulfated beef regular insulin. The overnight hypoglycemic reactions became even less frequent, and the insulin-binding capacity of her antibodies decreased to values seen in most patients who form antibodies to beef or pork insulin (5 mU/ml). The patient's hypoglycemic reactions were much less frequent, occurring only once or twice a week and almost always overnight. Her response to sulfated beef regular insulin was much more rapid than to human regular insulin with a more normal peak response to sulfated beef insulin given either subcutaneously (2 h) or intravenously (50 min). This clinical response to sulfated beef insulin was consistent with in vitro studies evaluating the relative avidity of her antibodies for beef, pork, human, and sulfated beef insulin (4). The relative avidities were: beef, 1.00; pork, 0.49; human, 0.42; and sulfated beef, 0.09.

Although the patient was receiving only sulfated beef insulin via an insuln infusion pump, her antibody levels again rose to levels consistent with immune-mediated insulin resistance (16 mU/ml). This may have been due to the fact that the epitope for the stimulation of antibody formation is not altered by sulfation. However, the patient's favorable clinical course did not change. She discontinued the pump several months later and is currently taking sulfated beef regular insulin before each meal and at ~0400 each morning. Her hypoglycemic episodes have decreased markedly, occurring approximately once per week.

At least four other similar patients have been reported (5–8). All had frequent and profound hypoglycemia and markedly increased insulin-binding antibodies. Our patient fulfilled the criteria for brittle diabetes (1). Although she did not have clinical insulin resistance (>200 U/day), her insulin-antibody levels were consistent with values associated with immune-mediated insulin resistance. Although one patient cannot constitute proof, it seems likely that the increased binding capacity of her circulating antibody caused her brittle diabetes by interfering with a predictable pattern of insulin action after injection. Instead, insulin was probably bound by her antibodies and released at unpredictable times, accounting for her rapid shifts between hyperglycemia and hypoglycemia. To circumvent this problem, the patient was given sulfated regular beef insulin. Sulfation of insulin masks the site recognized by the antibody but does not eliminate the biological activity of insulin. Therefore, as we had expected, sulfated beef insulin was less avidly bound to her antibodies, and her brittle diabetes rapidly improved despite the fact that the antibody values, although initially decreased, eventually remained elevated. In conclusion, recurring, unanticipated, and clinically unexplainable hypoglycemia can occasionally be due to very high levels of insulin antibodies occurring in patients who do not require very large doses of insulin. If this is the case, successful treatment is possible with sulfated beef insulin.

MAYER B. DAVIDSON, MD
DINESH KUMAR, MD
WESLEY SMITH, MD

From the Departments of Medicine, Cedars-Sinai Medical Center, University of California Los Angeles School of Medicine and University of Southern California School of Medicine, Los Angeles, California.

Address correspondence and reprint requests to Mayer B. Davidson, MD, Division of Endocrinology (B-131), Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Los Angeles, CA 90048.

REFERENCES

1. Tattersall R: Brittle diabetes. *J Clin Endocrinol Metab* 6:403–19, 1977
2. Gill GV, Walford S, Alberti KGMM: Brittle diabetes—present concepts. *Diabetologia* 28:579–89, 1985
3. Dixon K, Exon PD, Hughes HR: Insulin antibodies in aetiology of labile diabetes. *Lancet* 1:343–47, 1972
4. Kumar D: Immunoreactivity of insulin antibodies in insulin-treated diabetics: significance of the beta-chain carboxy-terminal amino acid (B-30) of insulin. *Diabetes* 28: 994–1000, 1979
5. Harwood R: Insulin-binding antibodies and "spontaneous" hypoglycemia. *N Engl J Med* 262:978–79, 1960
6. Renie A, Hamilton G, Adkinson NF Jr, Rendell MS: Hyperlabile diabetes accompanied by insulin resistance. *Clin Chem* 27:1463–64, 1981
7. Albert SG, Popp DA: Hypoglycemia due to serum-complexed insulin in a patient with diabetes mellitus. *Diabetes Care* 7:285–90, 1984
8. Van Haeften TW, Krom BA, Gerich JE: Prolonged fasting hypoglycemia due to insulin antibodies in patient with non-insulin-dependent diabetes mellitus: effect of insulin withdrawal on insulin-antibody–binding kinetics. *Diabetes Care* 10:160–63, 1987

Postpartum Progression of Diabetic Retinopathy

We would like to highlight the difficulties in the management of diabetic retinopathy through report of a patient whose rapidly progressing retinopathy was not well controlled during pregnancy and progressed postpartum despite laser treatment.

The patient was a 26-yr-old white woman who had had insulin-dependent diabetes for 16 yr. For 7 yr she had had intermittent proteinuria, which had persisted for 5 yr. She smoked 15–20 cigarettes/day. Her diabetes was managed with Actrapid 70/30 Penfill (Novo, Copenhagen) three times daily and Ultratard (Novo) at night.

At 7 wk gestation, she had bilateral spoke opacities in her lenses and two hemorrhages on her right fundus. Blood pressure was 140/80 mmHg, urinary protein excretion was 2.3 g/24 h and creatinine clearance 51 ml/min.

At 17 wk gestation, the patient complained of blurred vision and was found to have severe preproliferative