Hyperlabile Diabetes Accompanied by Insulin Resistance

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It is generally held that high insulin antibody concentrations, by "buffering" abrupt swings in free insulin concentrations after injections of exogenous insulin, tend to stabilize blood glucose variations in diabetic patients. However, we encountered a patient with extremely labile diabetes coexisting with insulin resistance. This patient's injections were switched to pure porcine insulin from his usual mixed bovine/porcine insulin, in an effort to decrease his insulin requirement. This treatment was successful, and, as his insulin dosage decreased, his diabetic lability diminished substantially. His diabetes was eventually considered stabilized on about 22 units of porcine insulin daily. The serial decrease in his insulin antibody concentrations, monitored by use of solid-phase radioimmunoassay, paralleled the disappearance of his diabetic lability as well as the decrease in his insulin requirement.

The injection of bovine/porcine insulin provides a potent antigenic stimulus for the development of antibodies. Antibodies to insulin usually appear in the serum of most insulin-treated patients within three months of beginning injections (1). Infrequently, insulin-antibody concentrations may increase to the point that a considerable fraction of injected insulin is antibody-bound and hence inactivated. This increases insulin dosage requirements and, when the requirement exceeds 200 USP units daily, immunologic insulin resistance is said to exist (2, 3). This condition represents a formidable clinical problem.

A quite different but equally severe problem is the condition known as hyperlabile or "brittle" diabetes, characterized by dramatic fluctuations in blood sugar—hypoglycemia alternating with extreme hyperglycemia (4). Usually the lability is refractory to even the most strenuous efforts to achieve good glycemic control with diverse insulin injection regimens, sometimes with three or more insulin injections spaced during the course of the day.

Immunologic insulin resistance and diabetic lability are usually considered to be mutually exclusive. In fact, it has been suggested that increased insulin antibodies, by "buffering" abrupt changes in free insulin concentrations induced by exogenous insulin injections, may serve to stabilize glycemic fluctuations (5). Indeed, there is evidence supporting the concept that "brittle" diabetes is usually associated with low concentrations of insulin antibodies (5).

Here we present a case of immunologic insulin resistance accompanied by hyperlabile diabetes. Insulin resistance was successfully treated by a switch to porcine insulin. As the insulin requirement decreased and insulin antibodies decreased, the diabetic lability gradually remitted. This case is offered as a counterexample to the conventional wisdom.

Case Report

A 33-year-old man was admitted to the Johns Hopkins Hospital in November, 1978, with diabetic ketoacidosis. He had first developed diabetes at age 22. Initially his blood glucose concentrations had been well controlled on 14 units of insulin daily, but his insulin requirement had progressively increased, particularly during the preceding two years. At the time of admission, he was taking 85 units of lente insulin and 15 units of regular insulin in the morning with 35 units of lente insulin plus 15 units of regular insulin before supper. During the past year, his diabetes had become extremely labile, severe hypoglycemic episodes alternating with extreme hyperglycemia. In the last few months before admission, he had had to make weekly visits to local emergency rooms because of either very high or very low blood sugar.

On physical examination, he was lethargic. There was no evidence of infection. At admission, the concentrations of clinical chemical analytes were: glucose 16.7 g/L, sodium 102 mmol/L, potassium 7.1 mmol/L, bicarbonate 5 mmol/L, chloride 98 mmol/L, and creatinine 26 mg/L. The arterial blood pH was 7.06.

Appropriate hydration and electrolyte replacement and an intravenous insulin infusion at a rate of 0.3 units/kg of body weight per hour were begun. He responded well with a decrease to a blood glucose concentration of 2.5 g/L during the next 24 h. In the belief that his diabetic lability might be due to the Somogyi phenomenon (i.e., hyperinsulinism), he was subsequently started on a low dose of lente insulin (16 units daily). This was unsuccessful: he slipped back into diabetic ketoacidosis, from which he was rescued by recommencing the intravenous insulin infusion. It was necessary to increase progressively his subcutaneous insulin dosage until he finally was receiving essentially the same dose as at the time of admission. He was discharged on this dose with instructions to adjust the dose according to urinary glucose readings, monitored with Clinistix tablets.

This management proved unsuccessful. Over the next month, his plasma glucose concentrations fluctuated from 200 mg to 9 g per liter, and he incurred several visits to emergency rooms. His total daily insulin dose was now about 200 units.

In an effort to decrease this high insulin requirement, we decided to switch the injections to pure porcine insulin.

Insulin-specific immunoglobulin G (IgG) antibody concentrations were determined by solid-phase radioimmunoassay as previously described (6), and were found to be very high (40 int. units of anti-bovine insulin IgG and 28 int. units of anti-porcine insulin IgG per liter). For three months, there was little change in diabetic lability, although the insulin requirement progressively decreased to about 75 units a day. Then, as the insulin requirement continued to decrease, the dramatic fluctuations in plasma glucose began to moderate (Figure 1).
Seven months after the switch to porcine insulin, his insulin dose had decreased to 30 units. His urinary glucose was now usually negative or trace by Clinitest. Plasma glucose concentrations varied between 1.5 and 2.5 g/L. There were no hypoglycemic episodes. Results of an assay for C-peptide performed at this time by methods previously described (7) were 0.028 mmol/L (normal value during fasting 0.4–0.5 mmol/L). Currently, his insulin dosage is 22 units daily. His glucose concentrations, although not perfectly controlled, are usually less than 2 g/L, and he no longer experiences hypoglycemic episodes.

Discussion

When first seen, this patient had hyperlabile diabetes despite stringent efforts at regulation by regular insulin coverage. Indeed, his diabetes defied efforts at control, even while he was hospitalized under close observation. The possibility of a Somogyi phenomenon was considered and disproved. We decided to switch from mixed bovine/porcine insulin to pure porcine insulin, in an effort to decrease his insulin requirement. The opinion at that time was that this patient had endogenously “brittle” diabetes, which would persist despite the expected decrease in insulin requirement. In fact, both the requirement for insulin and the diabetic lability diminished, correlating with the progressive decrease in antibodies to bovine and porcine insulin that resulted from the change to porcine insulin. Bovine insulin is more immunogenic than porcine insulin. Indeed, when bovine insulin is withdrawn, the concentrations not only of anti-bovine but also of anti-porcine and anti-human insulin antibodies decrease as a result of cross reaction (8). Eventually, the patient came under fair glycemc control on a dosage of two injections of insulin daily, totalling only about 30 units. He was no longer troubled by the original dramatic glycemc fluctuations with which he originally presented.

We explain his improvement as a consequence of a decrease in insulin-antibody concentrations. Optimal insulin effect depends on timed doses that “peak” in relation to meals and then diminish during the night, when there is no food intake. If antibodies act as a buffer, it is very clear that dissociation of insulin from the buffer “reservoir” need not follow the pattern of peaks and nadirs produced by the insulin injection regimen prescribed. Even “short-acting” insulin has a long enough half-life that insulin peaks no longer coincide with meals but in fact may well occur during the night, provoking hypoglycemia. In our patient, therefore, frequent injections of regular insulin would not be expected to succeed in controlling fluctuations in blood sugar. It was only after the concentration of antibody to insulin declined that changes in insulin dosage could be properly timed to correspond to impending changes in plasma glucose concentration.

Currently this patient no longer fits into the clinical category of “brittle” diabetes, despite endogenous insulin concentrations (as reflected by C-peptide values) near zero. He has benefited considerably from the switch to porcine insulin. In labile diabetic patients on high doses of mixed bovine/porcine insulin, insulin-antibody concentrations should be determined. If they are high, a change to pure porcine insulin is indicated and may lead to significantly improved diabetic control.

References