A Case of Maturity-Onset Diabetes Mellitus Resistant to Insulin but Responsive to Tolbutamide

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A nonobese patient with maturity-onset diabetes mellitus was hospitalized for treatment of an ulcer on his right foot. During this episode, his diabetic control worsened, and he proved unresponsive to exogenous insulin. Unresponsiveness to insulin persisted after healing of the ulcer. Tolbutamide therapy was then begun and produced a marked reduction in blood sugar levels. Withdrawal of the drug was accompanied by a progressive rise in blood sugar level. Intravenous infusion of regular pork insulin at rates of 45 U/h and single-component pork insulin at rates of 120 U/h had minimal effect on the blood sugar level. High levels of antibody to beef insulin were measured, with lower levels of pork insulin antibodies. C-peptide values were in a normal range before tolbutamide treatment and increased after use of the drug.

THE SYNDROME of insulin resistance in diabetic patients may be arbitrarily defined as an insulin requirement greater than 200 U/day. The most frequent causes of this resistance are obesity, infection, and the development of antibodies to insulin. Less common causes include lipoatrophic diabetes and antibodies to the insulin receptor (1, 2). The therapeutic approaches used in insulin-resistant diabetes include weight loss, treatment of infection, steroids, and the use of insulin of decreased antigenicity (3, 4). The use of oral hypoglycemic agents in nonobese insulin-resistant patients is uncommon. The present report describes the successful treatment of such a patient with tolbutamide.

Case Report

A 55-year-old white man with a 20-year history of diabetes mellitus was admitted to the Miami Veterans Administration Hospital with an ulcer on the dorsum of his right foot. For the first 6 years after discovery of his diabetes he had been treated with chlorpropamide, with fasting blood sugar levels between 100 and 140 mg/dl. Treatment had then been changed to NPH insulin, 20 units daily, maintaining fasting blood sugar levels in the same range for the next 6 years. Then a gradual rise in fasting blood sugar levels to the 250- to 300-mg/dl range led to discontinuance of insulin and the use of acetohexamide, 500 mg daily. In the several years before admission, his fasting blood sugar levels varied from 200 to 290 mg/dl. At no time were positive test results for ketones recorded.

On physical examination at the time of admission, he was a muscular man of large frame who was 175 cm tall. In the course of the previous 10 years, he had lost 32 kg from an initially obese status and now weighed 81 kg, this being about 5% above his ideal body weight (5). Physical findings included diffuse retinal microaneurysms; normal results of chest, cardiac, and neurologic examinations; absent pedal pulses on the left; and a posterior tibial pulse on the right. Initial laboratory values included a hematocrit volume of 37%, leukocyte count of 10 400 cells/mm^3 with 56 neutrophils and nine band forms, erythrocyte sedimentation rate of 110 mm/h, normal electrolytes, blood urea nitrogen value of 17 mg/dl with creatinine level of 1.2 mg/dl, and a plasma glucose of 300 mg/dl. Serum cholesterol was 180 mg/dl. Roentgenograms of the feet showed multiple small-vessel calcifications.

Treatment consisted of bed rest and antibiotics Acetohexamide was stopped and NPH insulin begun at a dose of 15 U daily. This dose was progressively increased as fasting blood sugar levels rose from an initial fasting value of 232 to about 300 mg/dl, with values at 1600 h attaining levels between 350 and 400 mg/dl. Ketones appeared in the urine in moderate to large amounts. Regular insulin was added in divided doses and progressively increased to levels exceeding 200 U daily with no effect; fasting blood sugar levels now averaged 350 mg/dl, with values at 1600 h varying from 470 to 600 mg/dl.

The ulcer began to heal; the leukocyte count and erythrocyte sedimentation rate normalized. Although ketones disappeared from the urine, fasting blood sugar levels remained at about 350 mg/dl, with levels at 1600 h ranging from 400 to 500 mg/dl. At this point, treatment was changed to regular pork insulin, gradually increasing from low levels until a total daily dose of 280 U had been reached with no change in urine or blood sugar levels. At this time tolbutamide, 500 mg daily, was added. A blood sugar sample drawn at 1600 h 1 day after tolbutamide therapy was begun was 330 mg/dl. Insulin was abruptly discontinued. Blood sugar levels declined progressively as tolbutamide was increased to 2 g daily (Figure 1a). Six days after the dose of tolbutamide was increased to 2 g, the fasting blood sugar level was 150 mg/dl with a level at 1600 h of 164 mg/dl. An increase in blood sugar levels ensued with discontinuation of tolbutamide (Figure 1a).

In order to confirm persisting insulin resistance, a continuous infusion of regular pork insulin was carried out 7 days after withdrawal of tolbutamide. By this time, his ulcer was healing well, leukocyte count and erythrocyte sedimentation rate were normal, and he had lost 5 kg since admission, now being within his ideal body weight range. The patient received breakfast; lunch was withheld. After baseline blood sugar measurements, the infusion was begun at a rate of 10 U/h and progressively increased over the next 2 h (Figure 1b, *left*). The infusion was terminated after a rate of 45 U/h had failed to measurably influence the blood sugar level. Over the course of the infusion, the blood sugar level dropped from 264 to 213 mg/dl. The day before (Day 16, Figure 1a), as control, the patient's lunch had been similarly withheld; and his blood sugar in late afternoon, without benefit of insulin, was 177 mg/dl. He was discharged on tolbutamide, 1 g twice daily. Outpatient random blood sugar levels averaged 140 mg/dl.

The mechanisms of insulin resistance and response to tolbutamide were explored via measurement of anti-insulin antibodies as well as measurement of C-peptide level (done by Dr. Arthur Rubenstein). Antibodies to both pork and beef insulin were ascertained by the technique of Berson and Yalow (6). Beef insulin antibody level was 185 mU/ml, this clearly in a range compatible with immunologic insulin resistance. Pork in-

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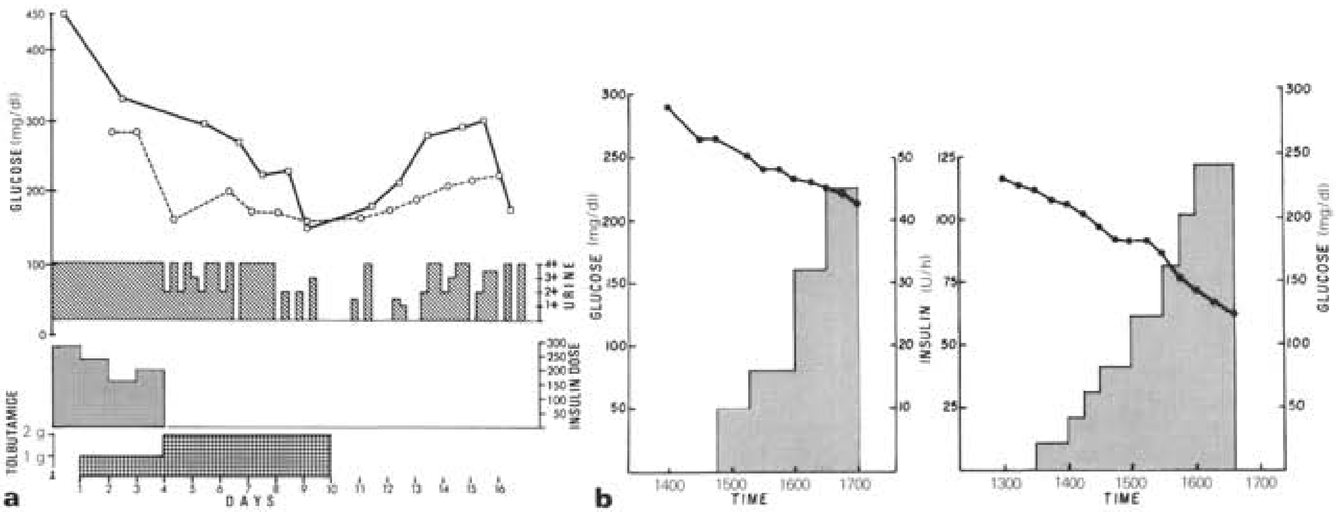

Figure 1a. Response to tolbutamide: The progressive response to tolbutamide is indicated as is the worsening of blood sugar levels on tolbutamide withdrawal. Urine sugar levels were measured by Clinitest® at 0400, 1000, 1600, and 2200 h and are so charted above. Blood sugar levels were measured fasting (*dashed line*) and at 1600 h (*solid line*). Insulin is charted as total daily dose. Please note that the low blood sugar level at 1600 h on Day 16 represents a value after lunch was omitted to serve as control for the insulin infusion the following day. **b.** Intravenous infusion of insulin: **Left.** After a fasting blood sugar of 214 mg/dl, the patient ate breakfast. Lunch was withheld. Three blood sugar samples were drawn before the infusion of regular pork insulin was begun. Blood sugar levels were measured at 15-min intervals. Insulin dose was progressively increased. **Right.** The infusion of single-component pork insulin was done in the same fashion as the preceding infusion. Note the linear fall of the blood sugar level as the infusion is increased. The blood sugar level at 1600 h on the preceding day with lunch omitted was 140 mg/dl.

sulin antibody level was 36 mU/ml, which despite being slightly elevated, perhaps as a result of cross-reaction with beef insulin antibody in the assay, was not in the same high range as the beef insulin antibody level. C-peptide levels were measured with the patient fasting and after he ingested a 400-cal Isocal® meal. Results are shown in Table 1. Before inception of tolbutamide treatment, two blood sugar measurements were done. Values were found to be in the high normal range. One month after tolbutamide therapy was begun, the fasting blood sugar level was unchanged. The postprandial level, however, was markedly increased beyond the normal range.

Because of the finding of elevated beef insulin antibody level with far lower levels of pork insulin antibody, it was felt that the resistance would respond readily to single-component pork insulin, which is quite effective in such circumstances (3, 4, 7). Accordingly, 1 month after discharge, the patient was rehospitalized for a trial of single-component insulin. The protocol followed the same lines as during the previous hospitalization. Tolbutamide was withdrawn for a period of 1 week. Lunch was withheld. After baseline blood sugar measurements, single-component insulin was infused at a progressively increasing rate, finally reaching 120 U/h (Figure 1b, *right*). Over the 3-h course of the infusion, the blood sugar level fell from 230 to 123 mg/dl. The slope of fall during infusion did not differ from that of the preinfusion period and did not change appreciably with increasing infusion rate. On the preceding day, as control, lunch was similarly omitted, and the blood sugar level at 1600 h of 144 mg/dl was no different from the value the succeeding day during the single-component insulin infusion. It was therefore concluded that single-component insulin had, at best, a minimal effect on this patient. Accordingly, he was discharged on 2 g of tolbutamide daily. Four months later, despite considerable weight gain, he continued to respond to the drug, with randomly measured blood sugar levels averaging 150 mg/dl.

Table 1. C-Peptide Values Before and After 1 Month of Treatment with Tolbutamide

	C-Peptide Values	
	Fasting	2 h Postprandial
	ng/ml	
Normal controls	1 to 3	3.5 to 6
Patient		
Before tolbutamide	4.9	5.8
	3.6	5.4
After tolbutamide	3.2	8.6

Discussion

This patient is clearly resistant to insulin as defined by the conventional criterion of insulin requirement exceeding 200 U/day. In addition, he failed to respond to a continuous infusion of regular pork insulin at a rate of 120 U/h. Although our use of continuous infusion of insulin in order to document resistance is new and therefore unstandardized, it may be compared to the use of continuous insulin infusion in diabetic ketoacidosis where infusion rates of 5 to 10 U/h decrease serum glucose level by 75 to 100 mg/dl · h (8-10).

The source of insulin resistance in this patient is somewhat unclear. Apparently neither obesity nor infection played a role, because at the time of insulin infusion he was at or very close to his ideal body weight, and his foot ulcer had healed. Insulin antibodies are implicated in the observed resistance, although pork insulin antibody levels were not in the high range of the beef insulin antibody levels. It is interesting that normal fasting and postprandial C-peptide levels were found before tolbutamide administration. This suggests that the patient's diabetic state may be caused, at least in part, by extrapancreatic factors, perhaps antibodies to his own endogenous insulin. In fact, treatment with exogenous insulin during the course of hospitalization may have exacerbated his underlying insulin resistance, thereby worsening his hyperglycemia (11).

Despite his resistance to exogenous insulin, this patient clearly responds to his endogenously produced insulin, and he had a marked response to tolbutamide. It would appear that the effect of tolbutamide was due, at least partially, to an enhancement of endogenous insulin production because, although basal C-peptide levels remained unchanged, the postprandial C-peptide was increased to supernormal levels 1 month after tolbutamide therapy was begun. This finding does not, of course, exclude additional extrapancreatic mechanisms of action of tolbutamide in this patient (12-14), particularly enhancement of insulin sensitivity.

Sulfonylureas are sometimes used with success in patients poorly controlled on insulin (15, 16). Such patients, however, are usually obese and, more importantly, do respond to insulin, albeit not to a therapeutically acceptable extent. Our patient differs from these previously described cases, first, by not being obese and second, by showing no response to exogenously administered insulin. There have been few attempts to assess the usefulness of sulfonylureas in nonobese diabetic patients not responding to insulin. That our patient may not be unique is suggested by Segre's report (17) of a similar case, although the degree of insulin resistance was not as fully documented. Sulfonylureas deserve further consideration as a mode of therapy for selected patients with maturity-onset diabetes resistant to exogenous insulin.

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References

1. Mabry CC, Hollingsworth DR, Upton GV, Corbin A: Pituitary-hypothalamic dysfunction in generalized lipodystrophy. *J Pediatr* 82:625-633, 1973
2. Flier JS, Kahn CR, Jarret DB, Roth J: Characterization of antibodies to the insulin receptor. A cause of insulin-resistant diabetes in man. *J Clin Invest* 58:1442-1449, 1976
3. Schlichtkrull J, Brange J, Christiansen AH, Hallund O, Heding LG, Jörgensen KH: Clinical aspects of insulin—antigenicity. *Diabetes* 21 (suppl 2):649-656, 1972
4. Galloway JA, Root MA: New forms of insulin. *Diabetes* 21 (suppl 2):637-648, 1972
5. Bray GA: The overweight patient. *Adv Intern Med* 21:267-308, 1976
6. Berson SA, Yalow RS: Quantitative aspects of the reaction between insulin and insulin-binding antibody. *J Clin Invest* 38:1996-2016, 1959
7. Yue DK, Turtle JR: New forms of insulin and their use in the treatment of diabetes. *Diabetes* 26:341-345, 1977
8. Page MM, Alberti KGMM, Greenwood R, Gumaa KA, Hockaday TDR, Lowy C, Nabarro JDN, Pyke DA, Sönksen PH, Watkins PJ, West TET: Treatment of diabetic coma with continuous low-dose infusion of insulin. *Br Med J* 2:687-690, 1974
9. Kidson W, Casey J, Kraegen E, Lazarus L: Treatment of severe diabetes mellitus by insulin infusion. *Br Med J* 2:691-694, 1974
10. Semple PF, White C, Manderson WG: Continuous intravenous infusion of small doses of insulin in treatment of diabetic ketoacidosis. *Br Med J* 2:694-698, 1974
11. Karam JH, Grodsky GM, Forsham PH: Insulin-resistant diabetes with autoantibodies induced by exogenous insulin. Successful treatment by insulin withdrawal. *Diabetes* 18:445-454, 1969
12. Feldman, JM, Lebovitz HE: Appraisal of the extrapancreatic actions of sulfonylureas. *Arch Intern Med* 123:314-322, 1969
13. Olefsky JM, Reaven GM: Effects of sulfonylurea therapy on insulin binding to mononuclear leukocytes of diabetic patients. *Am J Med* 60:89-95, 1976
14. Blumenthal SA: Potentiation of the hepatic action of insulin by chlorpropamide. *Diabetes* 26:485-489, 1977
15. Singer DL, Stewart RC, Hurwitz D: Chlorpropamide in patients on high insulin dosage. *N Engl J Med* 265:823-826, 1961
16. Mahler RJ: Diabetes mellitus. Distinguishing between patients receiving insulin and those requiring insulin therapy. *West J Med* 120:358-362, 1974
17. Segre EJ: Diabetes mellitus with insulin resistance: report of a case successfully treated with tolbutamide. *Metabolism* 11:562-565, 1962