

# Extreme Insulin Resistance: A Consequence of Insulin Switching?

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Insulin resistance can be due to several factors, among them, the presence of antibodies to insulin. Insulin antibodies are present in many diabetics after several months of therapy with insulin. Even the highly purified forms of insulin can result in antibody formation. In one series of diabetic patients on purified pork insulin, 52 percent of patients had detectable antibodies,<sup>1</sup> while in another series of patients on recombinant DNA human insulin, 10 percent had antibodies after one year.<sup>2</sup>

In most cases antibody formation is of no practical significance, but severe reactions are not rare and can include extremely high insulin requirements and anaphylaxis.<sup>3</sup> In one series of patients with high titers of insulin antibodies, 85 percent had a history of interrupted insulin therapy.<sup>4</sup> Insulin has a number of epitopes (sites of possible antibody formation), and human insulin shares many of these with insulins from other species. It is not surprising, then, to note that antibodies to insulin of one species can cross-react with human insulin.<sup>5</sup>

This report describes a patient with extremely high insulin resistance resulting from high titers of insulin antibodies, which in turn were thought to be related to switching between insulins of various sources.

## CASE REPORT

A 64-year-old woman complained of several days of nausea, vomiting, and weakness. Her blood glucose was 34.19 mmol/L (616 mg/dL) and serum acetone was 4+. Her arterial blood gases showed a pH of 7.14, an arterial partial pressure of oxygen (PaO<sub>2</sub>) of 12.5 kPa (94 mmHg), an arterial partial pressure of carbon dioxide (PaCO<sub>2</sub>) of 2.8 kPa (21 mmHg) and a bicarbonate of 7 mmol/L (7 mEq/L). Her physical examination was unremarkable except

for evidence of mild dehydration and moderate obesity; there was no acanthosis nigricans present, nor were there any stigmata of Cushing's disease. Laboratory data and radiological examination were likewise unremarkable except for minimally elevated serum lactic acid and minimally decreased serum magnesium levels.

The patient was begun on intravenous insulin, and the dose was titrated upward until the patient was on 1,000 units of insulin an hour. Slight further upward adjustment of the insulin resulted in precipitous drops in her serum glucose level and required, at different times, the administration of glucose infusions. This extreme resistance persisted for several days. An insulin antibody-binding immunoassay showed 49 percent of beef insulin and 46 percent of pork insulin was bound by the patient's serum; normal serum binds less than 3 percent of either type of insulin. The patient was begun on intravenous dexamethasone, and within three days her insulin requirements began to drop. At discharge, she was controlled on 34 units of recombinant DNA insulin and no longer required corticosteroid therapy.

The patient was a known diabetic who had been on mixed beef-pork insulin in the past. Her insulin source had been changed to recombinant DNA human insulin previously, but in the interim, on one occasion when hospitalized, she had again received mixed beef-pork insulin. She had been put back on recombinant DNA human insulin, but just before the present admission, she had received and used a prescription for mixed insulin.

## DISCUSSION

This patient had ketoacidosis, obesity, lactic acidosis, and hypomagnesemia, all of which could cause some insulin resistance, but not to this degree. There was no evidence of other disease states related to insulin resistance in this patient. The insulin resistance appears to be a result of her high titers of insulin antibodies.

Because this patient developed ketoacidosis and marked insulin resistance soon after changing back to mixed beef-

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pork insulin, her insulin antibodies appear to be related to her alternating between insulins of different sources. She received the equivalent of multiple challenges with an antigen. With the variety of insulins now available, an inadvertent change of insulin type could be made, particularly in situations such as admission to a hospital or nursing home. Physicians need to take extra precautions when a patient is transferred so that switching of insulin does not occur.

Previous reports have suggested that binding of insulin greater than 10 percent is associated with derangements in insulin pharmacodynamics.<sup>6</sup> This patient's high titer of antibodies resulted in marked insulin resistance, but at the same time, it appeared that once the patient's binding ability was saturated, further increases in insulin caused marked hypoglycemia. This hypoglycemia was difficult to control and became manageable only after corticosteroids were begun.

Corticosteroid treatment was able to reverse the insulin resistance to the point at which the patient's glucose levels came under control, and corticosteroid treatment has been

reported to be beneficial in certain other patients with high titers of insulin antibodies.<sup>7</sup>

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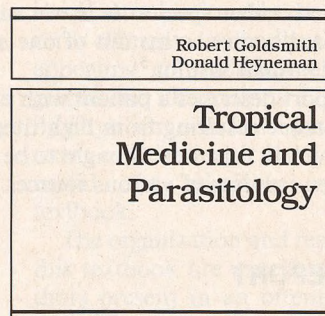
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