OBSERVATIONS

Immunological Insulin Resistance Due to Insulin Antibodies Developed After Cessation of Insulin Therapy in a Patient With Type 2 Diabetes

While insulin antibodies reportedly exist in about half of patients with type 2 diabetes who inject insulin, these antibodies do not often severely affect blood glucose levels (1). Here, we report a patient who had insulin antibodies against human insulin and developed insulin resistance after episodes of frequent hypoglycemic attacks, even though insulin therapy had been discontinued. A 68-year-old Japanese male was referred to our hospital because of hyperglycemia in October 2003. He weighed 89 kg, and his height was 171 cm. His levels of fasting plasma glucose, A1C, and urine C-peptide immunoreactivity were 313 mg/dl, 10.6%, and 38.7 μg/day, respectively. Anti-GAD antibody was negative, and insulin-binding capacity of serum was 3.9%. Insulin therapy (regular insulin 26 IU/day and NPH insulin 8 IU/day) was started, and his A1C levels ranged between 5.0 and 7.9% until May 2006, when he had frequent early-morning hypoglycemic attacks (blood glucose levels <40 mg/dl) that persisted even after insulin therapy was discontinued. His fasting serum insulin levels were >1,000 IU/ml, and insulin-binding capacity was 68.4%. Scatchard analysis of insulin antibody revealed that, similar to antibodies in patients with insulin autoimmune disease (2), the antibodies had a large capacity (binding capacity of the high affinity site 52.5×10^{-8}M) and low affinity (affinity constant $0.0227 \times 10^{8}M^{-1}$). Hypoglycemic attacks were prevented by having a snack at night, and administration of voglibose and metformin was started. His levels of fasting plasma glucose and A1C were ~70–140 mg/dl and ~6.3–8.1%, respectively, until June 2007, when his fasting plasma glucose levels suddenly increased to >300 mg/dl. Insulin-binding capacity was 91.1%, and Scatchard analyses of insulin antibody revealed that binding capacity was further increased compared to that in May 2006. His urine C-peptide immunoreactivity was 62.2 μg/day. Either regular insulin or insulin analog (lispro, aspart, or glargine) was given up to 48 IU/day, but control of blood glucose levels was difficult. In order to reduce insulin antibodies, double filtration plasmapheresis and plasma exchange were performed over 2 weeks, and administration of prednisolone (20 mg/day) was started in August 2007. His blood glucose levels were controlled with recombinant IGF-I instead of insulin until October 2007, when insulin therapy (aspart) was restarted. Insulin-binding capacity was decreased over time, and the amount of prednisolone administered was gradually reduced. Insulin therapy was withdrawn in January 2008, when the insulin-binding capacity was 64.4%, and his A1C levels remained at 4.8–8.3% until July 2008.

While it is widely accepted, based on the assumption that endogenous insulin would be less immunogenic, that cessation of insulin therapy is effective at reducing insulin antibodies induced by insulin therapy (3,4), our case demonstrates that insulin antibodies can increase even after insulin therapy is discontinued, suggesting that endogenous insulin can also stimulate the immune system. In such cases, administration of steroid hormone in combination with plasma exchange or plasmapheresis (5) in order to decrease insulin antibodies should be considered.

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