

OBSERVATIONS

A Case of Type 1 Diabetes With Nocturnal Hypoglycemia After Desensitization Therapy for Insulin Allergy

Antibodies against exogenously injected insulin are common with insulin treatment but seldom have serious effects on blood glucose (1). In insulin autoimmune syndrome (IAS), however, the insulin antibody causes hypoglycemia (2) in the absence of exogenous insulin treatment.

Here, we report a case of type 1 diabetes with insulin antibody, whereby the patient developed nocturnal hypoglycemia after desensitization therapy for an insulin allergy.

After receiving insulin therapy for 1 year, a 61-year-old man was admitted to our hospital because of an insulin allergy and poor control of diabetes. He had an itchy eruption at the insulin injection site. At the time of admission, the patient presented with an HbA_{1c} level of 16.2% (154 mmol/mol); anti-GAD antibody 80.0 U/L (<1.5 U/mL); serum C-peptide level 0.01 ng/mL after glucagon injection (fasting 0.67–2.48 ng/mL); and insulin-specific IgE 41.5 UA/mL (<0.34 UA/mL). He tolerated three daily injections of NPH insulin because it produced a lesser reaction than other insulin or its analogs. In fact, almost all human insulin or insulin analogs caused a skin reaction during the skin test, whereas protamine, zinc, and glycerol did not. We therefore diagnosed him with an insulin allergy and initiated desensitization using an increasing dose of human regular insulin, according to the procedure reported by Hayashi et al. (3). Following desensitization with up to 4.0 U of regular insulin, the patient's skin reaction to insulin

improved and he was able to tolerate insulin injections four times daily. However, at the same time, he developed nocturnal hypoglycemia. We subsequently reduced his bed-time dose of NPH insulin and finally stopped the treatment. We examined the binding kinetics of his insulin antibody using serum samples before and after desensitization.

Scatchard analysis revealed two binding components (high [K₁] and low [K₂] affinity), although the former (i.e., K₁) principally reflects each antibody's affinity as reported previously (4). Before desensitization, the affinity constants (K₁) and binding capacities (b₁) for the high-affinity components were K₁ 9.19 × 10⁻² (1/10⁻⁸ M) (insulin antibodies in patients with diabetes who are treated with insulin, 1.45–7.11) and b₁ 199 (10⁻⁸ M) (insulin antibodies in patients with diabetes who are treated with insulin, 0.08–1.1) (4), suggesting that the antibody had relatively low affinity (i.e., smaller K₁) but high capacity (i.e., larger b₁) for insulin binding. Interestingly, after the desensitization therapy, K₁ and b₁ values changed to 4.37 × 10⁻⁴ (1/10⁻⁸ M) and 424 (10⁻⁸ M), respectively, indicating that the binding affinity had been attenuated further. The kinetics after desensitization is comparable to that reported in patients with IAS (4). In IAS, although the autoantibody binds to a large amount of insulin with a resulting high capacity, the insulin-autoantibody complex is considered to become unstable and uncouples suddenly, leading to a hypoglycemic attack. Accordingly, in this particular case, this shift in binding kinetics after desensitization may account for the nocturnal hypoglycemia.

The increased concentrations of blocking antibodies that inhibit IgE-facilitated binding of allergens to B cells are one mechanism for desensitization (5). In our case, it is possible that insulin desensitization therapy induced these blocking antibodies with properties similar to those in IAS.

In summary, we observed hypoglycemia induced by insulin desensitization therapy. Desensitization therapy is the standard treatment for patients with insulin allergy. It must be recognized, however, that the characteristics of the insulin

antibody could be altered by desensitization therapy to that of an antibody observed in IAS.

TAKUMI KITAMOTO, MD
KENICHI SAKURAI, MD, PHD
KAORI TACHIBANA, MD, PHD
HIDETAKA YOKOH, MD
KO ISHIKAWA, MD, PHD
TAKASHI MIKI, MD, PHD
KOUTARO YOKOTE, MD, PHD

From the Department of Diabetes, Metabolism and Endocrinology, Chiba University Hospital, Chiba, Japan. Corresponding author: Kenichi Sakurai, kenichis-cib@umin.org.

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