





A case of type 1 Diabetes mellitus unresponsive to insulin glulisine

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ABSTRACT

A 29-year-old man applied to the internal medicine outpatient clinic with fatigue and high plasma glucose levels. He had type 1 Diabetes Mellitus for 10 years and was using insulin glargine U300 and insulin glulisine for treatment. His glycosylated hemoglobin level was 16.7%, and he was hospitalized. Insulin doses were calculated as 1 unite/kg /day; glulisine 3×8 unit/day and glargine U300 1×18 unit/day were ordered. Although we increased the total insulin dosage to 1,5 units/kg/day, the plasma glucose measurements did not improve. The short-acting insulin analog was switched to insulin aspart based on the fact that insulin autoantibodies might cause this situation. On aspart treatment, the patient suffered from hypoglycemia with the same doses of glulisine. The occurrence of insulin autoantibodies against glulisine was confirmed clinically. Basal insulin dose was reduced to 20 units, and aspart 3×6 units/day was enough for plasma glucose control. Hyperglycemia due to autoantibodies against analog insulins is very rare. This rare case report must be kept in mind in hyperglycemic patients with a history of long-time analog insulin treatment.

Keywords: hyperglycemia, type 1 Diabetes mellitus, insulin autoantibody

INTRODUCTION

Hyperglycemia due to autoantibodies against analog insulins is very rare. Here we report a type 1 Diabetes Mellitus patient who was on glulisine treatment for 10 years, and whose blood glucose measurements deteriorated recently. Hyperglycemia was regulated after the insulin switch from glulisine to aspart.

CASE

A 29-year-old male patient has been admitted Internal Medicine outpatient clinic with complaints of fatigue and high blood glucose levels. He had type 1 Diabetes Mellitus for 10 years and Juvenil Idiopathic Arthritis for 17 years. It was learned that he was using insulin glargine U300 24 units per day and preprandial insulin glulisine 8 units three times a day. His physical examination was as follows. Height was 165 cm, weight was 50 kg and body mass index was 18,3 kg/m². He was conscious, cooperative, and oriented. There were no signs of dehydration and /or acetone odor. The Head and neck examination was normal. Cardiovascular and respiratory system examination was normal. The abdomen was not tender and organomegaly was not found.

Venous plasma samples were obtained. His plasma glucose was 431 mg/dl. Urinary ketones were positive but blood pH and bicarbonate levels were normal. Complete blood count, C reactive protein, renal and hepatic tests were normal.

Glycosylated hemoglobin (HbA1c) level was 16.7%. He had proliferative diabetic retinopathy and sensory neuropathy.

His total insulin dosage was calculated according to the 1 unit/kg/day target. Insulin glulisine 3x8 units and insulin glargine U300 18 units/day were started. Capillary glucose measurements were done 7 times a day and insulin doses were titrated, but his glucose levels could not be regulated despite high insulin doses. Meanwhile, the patient's source of infection, fever, and accompanying causes of acute blood sugar elevation were reviewed. No pathology was detected. The patient's dietary compliance was specifically reviewed and controlled. It was observed that the patient complied with his diet. Insulin injection sites were checked and no pathology that could cause malabsorption or distribution was found. The insulin injection technique was reconsidered. Despite 1,5 unit/kg/day insulin dosage, his blood glucose measurements did not change.

Considering that insulin autoantibodies may have developed, insulin glulisine was discontinued and the rapid-acting insulin analog insulin aspart was started instead. The patient developed hypoglycemia with the same doses, and the diagnosis of antibodies against insulin glulisine was clinically made. The patient's insulin glargine U300 treatment was continued by reducing the dose to 20 units per day. Blood sugar regulation was achieved with insulin aspart 6 units 3 times a day.

The insulin antibody result was 5% (reference range <8.2%). Since specific antibody against insulin glulisine has not been

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Date	Capillary glucose levels (mg/dl)							Preprandial insulin	Glargine U300
Hour	06.00 preprandial	08.00 postprandial	11.00 preprandial	13.00 postprandial	17.00 preprandial	19.00 postprandial	21.00	Glulisine unit	Unit
2.7.2021	368	380	343	355	341	362	292	3×8	34
3.7.2021	143	154	321	360	370	381	300	3×10	34
4.7.2021	99	143	321	365	370	375	300	3×14	34
								Aspart unit	
5.7.2021	118	130	329	335	264	298	192	3×10	30
6.7.2021	68	98	100	142	106	137	102	3×8	20
7.7.2021	149	152	102	132	106	130	100	3×6	20

studied in our country, they could not be detected. 2 months later, it was determined that the patient's capillary plasma glucose levels were still on target and the HbA1C level had decreased to 9%.

The patient's capillary glucose monitoring results and insulin doses are summarized in **Table 1**.

DISCUSSION

The development of autoantibodies against insulin and related blood sugar irregularity have been reported during the use of animal insulin. However, with the introduction of analog insulins, the development of insulin autoantibodies against these new insulins has been rarely reported (1). Since the insulin-specific antibody used in this case was not studied in our country, it could not be detected, but a clinical diagnosis was made.

Insulin autoimmune syndrome is a clinical condition that occurs as a complication of insulin therapy in people receiving regular insulin therapy and results in severe insulin resistance. In these people, high anti-insulin antibody titers are detected and blood sugar regulation can be achieved by temporarily switching to another insulin. It is recommended to use 60-80 mg/day of prednisone for 2-3 weeks in refractory cases (2).

In the literature, a Type 2 DM patient with fasting hypoglycemia and postprandial hyperglycemia, which presents similar to the endogenous insulin autoimmune syndrome, has been reported. The fluctuations in the blood sugar of the patient were controlled by discontinuing this used insulin and starting medical treatment that stimulates endogenous insulin secretion (3). In another recent case report, a patient with the development of antibodies against exogenous insulin use and the development of hypoglycemia similar to insulin autoimmune syndrome is presented (4).

It was stated that insulin was switched in the management of the patient, but when the hypoglycemia attacks could not be controlled, oral prednisone treatment was administered for 3 weeks and the treatment was provided (4).

In the case report of another patient with Type 2 DM who was diagnosed with Type B insulin resistance, it was shown that the patient was treated with rituximab, dexamethasone, and cyclophosphamide, and blood sugar regulation was achieved with metformin and pioglitazone after the treatment (5). Type B insulin resistance is a clinical condition that is more common in women aged around 40 years and in the black race, occurs with the presence of autoantibodies against the insulin receptor, postprandial hyperglycemia is observed despite the use of very high units of insulin, and, paradoxically, fasting hypoglycemia can also be seen (6,7). In our patient, the diagnosis of Type B insulin resistance was ruled out because of

the absence of acanthosis nigricans, absence of autoimmune markers, and normal inflammatory markers. However, Type B insulin resistance could not be completely excluded because the patient was diagnosed with juvenile idiopathic arthritis. It was thought that inflammatory pathways and acute phase response might have been suppressed because he used etanercept with this diagnosis.

Since the insulin antibody level was found to be normal in our patient and he did not need high doses of insulin as stated in the literature, insulin autoimmune syndrome was also excluded. Moreover, when the capillary plasma glucose measurements of the patient were examined, it was observed that the capillary plasma glucose of the patient was around 300 mg/dl, no matter how many units of insulin glulisine were administered. From this, it was concluded that the patient was only under the effect of basal insulin and had no response to rapid-acting insulin. After switching from insulin to aspart, the patient's plasma glucose values decreased rapidly, the basal insulin dose was reduced and the patient was regulated metabolically.

In the literature, another case that was unresponsive to insulin glulisine and whose insulin antibody was negative and whose plasma glucose control was achieved by changing aspartate could not be found. Therefore, we think that our case will contribute to the literature. Our limitation regarding this case is that the specific antibody level could not be demonstrated. Since the insulin-specific antibody used in this case was not studied in our country, it could not be detected, but a clinical diagnosis was made. Unfortunately, this situation is related to the fact that we do not have such an opportunity technically.

CONCLUSION

We think that it should be kept in mind that there may be insulin-specific unresponsiveness, especially in patients who use analog insulin for a long time, when they apply with a hyperglycemic emergency or when plasma glucose control is progressively impaired.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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