

Autoantibodies to Insulin and Dysglycemia in People With and Without Diabetes: An Underdiagnosed Association

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The potential effects of inhibitory immunoglobulins to insulin were first described in insulin-treated patients many decades ago (1). This antibody response is thought to occur in at least 40% of patients on insulin therapy (2). Subsequent case reports documented glycemic excursions in the form of markedly increased insulin requirements and unpredictable hypoglycemic episodes, both of which were attributable to insulin autoantibodies (3).

Autoantibodies to insulin also can occur occasionally in patients who have not been previously exposed to insulin. Autoimmune hypoglycemia resulting from high titers of insulin autoantibodies have been reported, mostly from Japan, as a rare cause of hyperinsulinemic hypoglycemia (4). There has only been one confirmed case of autoimmune hypoglycemia reported from India (5). The estimation of insulin autoantibodies is an integral part of the diagnosis in such cases.

Apart from insulin, other inciting agents implicated include sulfahydryl group-containing drugs and alpha-lipoic acid (ALA). Autoimmune hypoglycemia also has been reported to be associated with autoimmune disorders and plasma cell dyscrasias (6). Spontaneous resolution has been reported in a few cases of autoimmune hypoglycemia, and a dramatic response to steroids was seen in some other cases that manifested both hypoglycemia and hyperglycemia.

In this article, we describe our experience with patients who presented with glycemic excursions resulting from insulin autoantibodies from a single university referral teaching center in South India.

Spontaneous Hyperinsulinemic Hypoglycemia

Case Presentation

At the Department of Endocrinology of Amrita Institute of Medical Sciences in Kochi, Kerala, India, a large tertiary care center, between 2008 and 2014, we diagnosed eight cases in which insulin autoantibodies could be implicated as the etiological factor responsible for spontaneous hyperinsulinemic hypoglycemia. One patient presented exclusively with postprandial hypoglycemia-related symptoms, whereas the others presented with a combination of fasting and postprandial symptoms. During the same time period, there were only seven cases of histopathologically proven insulinomas diagnosed in our center.

All the patients underwent a mixed-meal challenge test, followed by a supervised fast. Samples were collected to measure insulin and C-peptide when the patients were symptomatic, with blood glucose levels of <55 mg/dL. Insulin autoantibodies were estimated by radiobinding assay. A postprandial rise of glucose after the mixed meal was demonstrable in all patients. Imaging of the pancreas by a multi-detector computed tomography

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TABLE 1. Clinical and Biochemical Details of Eight Patients With Autoimmune Hypoglycemia

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)/sex (F/M)	69/F	28/F	60/M	62/F	65/M	42/F	66/M	41/M
Symptoms: postprandial (P), fasting (F), or combined (C)	P	F	C	P	C	P	F	C
Duration of symptoms (months)	2	2	2	3	3	1	3	3
Inciting agent	ALA	Carbimazole	None	None	None	None	None	None
Insulin (μ IU/mL)	68.5	1,410	163	113	>300	73	>300	10,080
C-peptide (ng/mL)	5.6	2.9	2.3	5.2	9.3	7.2	6.2	20
Insulin autoantibodies (normal <0.4 U/mL)	>50	>300 (ELISA)	>50	>50	>50	>50	>50	>50
Other relevant results								
Serum electrophoresis	No M band		No M band	No M band	No M band		No M band	
Antinuclear antibody testing	Negative							
Remission characteristics: spontaneous (S) or after oral prednisolone for 3 months (P [dosage])	S	S	S	P (20 mg)	P (20 mg)	S	P (40 mg)	P (40 mg)

M band, monoclonal protein band, a serum electrophoresis finding suggestive of multiple myeloma.

pancreatic protocol was also performed. Other relevant investigations such as serum protein electrophoresis were done to exclude myeloma and benign gammaglobinopathy in older patients. Endoscopic ultrasound was performed in three patients. Interestingly, urine ketones were positive in two patients during the 72-hour fasting.

Insulin was estimated by chemiluminescent microparticle immunoassay with an analytic sensitivity of <1 μ IU/mL. C-peptide was estimated by electrochemiluminescence immunoassay on the Elecsys system (Roche Diagnostics, Mannheim, Germany) with an analytical sensitivity of 0.01 ng/mL. Insulin autoantibodies were estimated by radiobinding assay in Quest Diagnostics (Nichols Institute, San Juan Capistrano, CA). Less than 0.4 U/mL was considered an undetectable titer. In one patient, insulin antibody estimation was carried out by enzyme-linked immunosorbent assay (ELISA; positive: >15 U/mL).

Table 1 provides patients' clinical and biochemical details.

Onset was abrupt in all eight patients. In one patient, the inciting agent was carbimazole prescribed for Graves' disease. In another patient, ALA, which was used as a health supplement, could be implicated. Patients with less severe presentations had spontaneous remission within 3 months. All of the severe cases responded to steroid therapy at doses of 0.5–0.75 mg/kg/day, which were tapered and stopped within 3 months. None of the patients had a recurrence. Three patients had other autoimmune comorbid diseases (patient 2: Graves' disease, patient 3: pernicious anemia and autoimmune hypothyroidism, and patient 7: autoimmune hypothyroidism).

Glycemic Fluctuations in People With Diabetes Taking Insulin

Case 1 Presentation

A 67-year-old woman with type 2 diabetes for the past 10 years, previously well controlled on oral hypoglycemic

agents, presented with diabetic ketoacidosis (DKA) precipitated by a urinary tract infection, for which she was started on insulin. One month after starting insulin, she had recurrent nocturnal hypoglycemic episodes with postprandial hyperglycemia. The basal component of her basal-bolus insulin regimen was then stopped, but even while only using an ultra-short-acting analog insulin at dinner, she had documented early-morning hypoglycemia. Despite discontinuing insulin for 72 hours, she continued to experience nocturnal hypoglycemia with random venous plasma glucose of 54 mg/dL. A critical sample showed an insulin level of 1,901 μ IU/mL and C-peptide level of 11 ng/mL, which ruled out exogenous insulin-related hypoglycemia. Several postprandial glucose levels were >400 mg/dL. She was then suspected to have autoimmune hypoglycemia. Insulin antibodies were elevated >50 U/mL. She was started on prednisolone 0.5 mg/kg and two doses of short-acting insulin before breakfast and lunch. She

had a partial remission at the end of 2 weeks; 6 weeks after initiation of treatment, she had a full remission, and the steroids were tapered.

Case 2 Presentation

A 75-year-old man with type 2 diabetes for 6 years who was on insulin therapy for the past 4 years was detected to have carcinoma of the colon 1 year before presentation. He underwent a hemicolectomy and was later diagnosed with liver metastasis and cirrhosis of the liver. He was on bvacuzumab and chemotherapy for the disease, which was staged as T4 M1. His glycemic control was erratic 1 month before presentation, and he was admitted with DKA five times during this period and once had lactic acidosis requiring dialysis. His blood glucose was controlled only with intravenous insulin infusion; when he was shifted back to subcutaneous insulin, he slipped back into DKA.

At presentation, he was on degludec and three-times-daily short-acting insulin. His random blood glucose was 520 mg/dL, and his DKA was severe, with a pH of 6.9 and bicarbonate of 3 mEq/L. He was managed with routine care, but for the unremitting acidosis, he required hemodialysis. His glucose was not controlled even with 100 units/hour of intravenous insulin, and his blood glucose values ranged from 600 to 700 mg/dL.

Considering the possibility of antibody-mediated insulin resistance, steroids were started after sending a serum sample for insulin antibody testing. Within 4 hours of the first hydrocortisone dose, his glucose decreased to <500 mg/dL, and within 24 hours of starting steroids, his DKA resolved. He was switched to prednisolone 1 mg/kg/day and was on multiple subcutaneous doses of short-acting analog and degludec insulin. With this regimen, his glycemic control was satisfactory. Subsequently, he was on tapering doses of steroids with reasonable glycemic control. He has been restarted on chemotherapy with panitumab.

Questions

1. In what clinical circumstances should insulin autoantibody syndrome be suspected?
2. What are the biochemical and hormonal indicators of autoimmune hypoglycemia?
3. What are the available management strategies for dysglycemia resulting from insulin autoantibodies?

Commentary

We described above two scenarios in which we believe insulin autoantibodies played a pathogenic role—patients without diabetes who have hyperinsulinemic hypoglycemia and those with diabetes who have wide glycemic excursions on insulin. These cases offer insights that may be useful in the management of similar cases in resource-limited settings.

Autoimmune responses and their propensity for leading to disease states are well known. It is, however, very rare for a protein hormone to elicit an antibody response and still rarer for that response to manifest as clinically important states beyond assay interferences. Some HLA class II subtypes, especially DRB10406, DQA10301, and DQB10302, are known to be associated with insulin autoantibody responses (7). Drugs containing sulfhydryl groups are thought to interact with the disulfide bond in insulin and make it immunogenic. Methimazole therapy and ALA use, both of which contain sulfhydryl groups, were probable inciting agents in our case series. Autoimmune diseases are also known to be associated with insulin autoantibodies (6). In the majority of cases, however, these antibodies do not cause any clinical effects. Patients with autoimmune diseases such as pernicious anemia and autoimmune thyroid disease were present in our series. We screened all patients >50 years of age for monoclonal gammopathies because hypoglycemia may precede the clinical manifestation of myeloma by many years.

Insulin autoantibodies are mostly polyclonal in origin and are mostly of the immunoglobulin G class. They can be of high affinity/low binding capacity or low affinity/high binding capacity (8). The latter is often associated with clinical manifestations. These antibodies are virtually indistinguishable from the antibodies seen in up to 70% of children with type 1 diabetes. When the antibody titers are very high, there may be clinical manifestations resulting from the ability of these antibodies to act as temporary storehouses of insulin, which prevents its action, and then the subsequent release of the stored insulin, which causes hypoglycemia. This explains the characteristic increase in blood glucose in the immediate postprandial period and the hypoglycemia observed later. Possible alternative explanations include direct stimulatory effects of the antibodies on the pancreas and the crosslinking of insulin-insulin receptor complexes by the insulin antibodies, resulting in potentiation or prolongation of insulin action (6).

Patients with exclusive postprandial symptoms might be mislabeled as having reactive hypoglycemia if antibodies are not checked. This is especially relevant in that current Endocrine Society guidelines caution against testing for insulin and C-peptide, even in cases involving symptoms in the course of a mixed-meal test (9). An individualized approach is probably the answer. In symptomatic patients with documented hypoglycemia, testing for insulin and C-peptide is of value. Classically, insulin autoantibody syndrome is associated with insulin levels >100 μ IU/mL, which was true in all but one of our patients.

The use of exogenous insulin itself elicits antibodies, and the detection of antibodies alone does not suggest that they are pathogenic. However, in the first case we presented of an insulin-using person with diabetes, the very high insulin and C-peptide levels and subsequent response to ste-

roids suggest that the autoantibodies were pathogenic. In the second case presentation of a person with diabetes using insulin, the patient had cirrhosis of the liver and was treated with insulin, both of which can be associated with autoantibodies (6). The patient's extreme insulin resistance and dramatic response to steroids point to the antibodies as the culprit in this case.

In summary, we share our experience with insulin autoantibody syndrome, which can manifest as hypoglycemia, hyperglycemia, or both. Autoantibodies probably need to be ruled out in all cases of documented symptomatic postprandial hypoglycemia to avoid misdiagnosing this syndrome as reactive hypoglycemia. In our center's experience, this entity appears to be more common than insulinoma as a cause of noniatrogenic hyperinsulinemic hypoglycemia.

Clinical Pearls

- Autoimmune hypoglycemia is a differential for patients with documented reactive hypoglycemia and very high insulin levels.
- Postprandial increase in glucose during a mixed-meal test can point toward an autoimmune etiology, especially in resource-limited settings where there are limitations on imaging and sulfonylurea estimation.
- Recent onset of extreme insulin resistance with a very high insulin requirement, especially with unpredictable hypoglycemia, can be a feature of insulin autoimmunity syndrome.
- In most cases of autoimmune-related glycemic excursions, the response to steroid treatment is dramatic.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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