

Clopidogrel Induced Autoimmune Hypoglycemia

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Abstract

We report insulin autoimmune syndrome in a diet-controlled type 2 diabetes mellitus patient. She developed recurrent attacks of severe hypoglycemia 1 week after the initiation of clopidogrel. The evaluation revealed high insulin and C-peptide levels consistent with hyperinsulinemic hypoglycemia. The insulin-to-C-peptide ratio was reversed and >50. Anti-insulin antibody titers were highly positive.

Keywords: Clopidogrel, hyperinsulinemic hypoglycemia, insulin autoimmune syndrome, severe hypoglycemia, type 2 diabetes mellitus

INTRODUCTION

Hyperinsulinemic hypoglycemia in patients with diabetes, and no history of bariatric surgery, is likely related to treatment, insulinoma, extrapancreatic tumors, and autoimmune hypoglycemia.^[1-3] We report an interesting patient with hypoglycemia in a diet-treated type 2 diabetes (T2D).

CASE REPORT

A 67-year-old Emirati woman with diet-controlled T2D, hypertension, hyperlipidemia, gastroesophageal reflux disease, idiopathic hypercalciuria, and kidney stones developed episodes of recurrent symptomatic hypoglycemia mainly 2–4 h after meals, in addition to few incidents of fasting hypoglycemia. Baseline laboratory assessment confirmed normal thyroid, renal, and liver function tests with glycated hemoglobin of 6.1% (43.2 mmol/mol).

During 60 h of supervised fast, the patient's blood glucose failed to drop below 4.8 mmol/L (88 mg/dl). However, 4 h after a mixed meal, she developed symptomatic hypoglycemia with serum glucose of 2.7 mmol/L (48 mg/dL) [Figure 1]. Insulin level was 2000 uIU/mL (2.6 – 24.9 uIU/mL), and C-peptide levels 1.7 ng/mL (0–1.2 nmol/L). Additional testing confirmed no intake of insulin secretagogues and negative ketones.

Repeated testing 2 h after breakfast on the following day demonstrated a blood glucose level of 196 mg/dl. Total and free insulin measured by chemiluminescent immunometric assay at LabCorp, USA, were 2976 uIU/mL and 57 mIU/mL, respectively (normal total insulin for fasting

adults is 0–17 uIU/ml, and normal 2-h total insulin after the meal is 16–166 uIU/mL); C-peptide level was 3.61 nmol/L (<1.2). Proinsulin level was 77.3 pmol/L (0–10) and anti-insulin antibody titer was >625uU/mL (normal <5) [Figure 2].

The patient's medications included: indapamide SR*1.5 mg daily, losartan 50 mg daily, and atorvastatin 20 mg daily, in addition to clopidogrel that was started 7 days before the incidence of hypoglycemia. The patient was not exposed to insulin or insulin secretagogues previously.

Clopidogrel was switched to aspirin, and the patient was treated with acarbose, an alpha-glucosidase inhibitor, to slow the absorption of carbohydrates and minimize postprandial glucose spikes, in addition to prednisone 40 mg daily. The patient reported a rapid resolution of her hypoglycemia within 2 days [Figure 2].

Monitoring total insulin level, free insulin and anti-insulin antibody titers revealed a steady decline over the next few months [Figure 2]. Glucocorticoid dose was tapered off over 7 months. Two months after discontinuing prednisone, the patient did not have any further hypoglycemic episodes. Total insulin and insulin antibody levels remained in the normal range.

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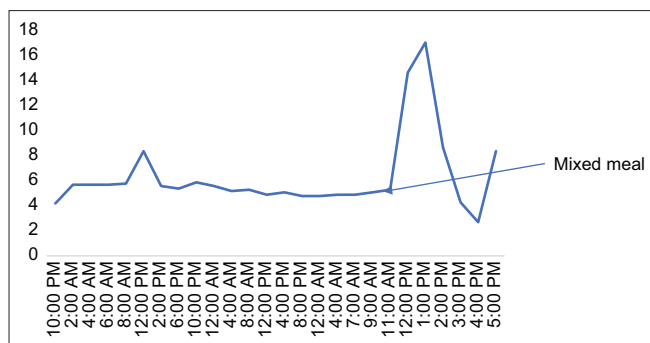


Figure 1: Blood glucose changes during prolonged fasting and after a mixed meal

DISCUSSION

To our knowledge, this is the first case report of insulin autoimmune syndrome (IAS), also known as Hirata disease, causing hypoglycemia in an Emirati patient following clopidogrel exposure.

In our patient, Whipple's triad of symptomatic hypoglycemia and resolution following glucose/food intake were documented before the initiation of medical evaluation.^[2-4] The occurrence of fasting and postprandial hypoglycemia was confirmed by continuous glucose monitoring. The diagnosis of hyperinsulinemic hypoglycemia was confirmed by simultaneous low blood glucose, elevated insulin, proinsulin, and C-peptide levels. The mismatch between the insulin and C-peptide pointed to the likelihood of the existence of insulin antibodies. The finding of high insulin antibodies clinched the diagnosis of IAS.

Although patients with IAS typically experience symptoms of mild and transient hypoglycemia a few weeks after exposure to medications containing a sulfhydryl group,^[5] our patient had recurrent severe incapacitating hypoglycemic attacks after her sixth dose of clopidogrel.

There have been few case reports of IAS during clopidogrel therapy.^[5-8] The proposed explanation for hypoglycemia is that the clopidogrel sulfhydryl group interacts with the insulin molecule's disulfide bond, rendering it immunogenic. Consequently, insulin autoimmune antibodies (IAAs) produced circulate in the blood.^[9] Another Interesting case was reported recently in this journal. Spontaneous hypoglycemia after starting carbimazole due to insulin autoimmune syndrome, characterized by high levels of insulinemia and circulating autoantibodies to insulin without prior insulin administration was described from Saudi Arabia.^[10]

During fasting, IAAs are not fully occupied, and free insulin concentrations are low. Insulin secreted after meals typically binds to the available IAAs and is metabolically ineffective, leading to postprandial hyperglycemia. Insulin will, however, be released from the IAA-insulin complexes when all sites are occupied, causing hypoglycemia.^[11] An alternative mechanism for hypoglycemia is developing antibodies to the insulin antibody resulting in the direct activation of insulin receptors.^[12]

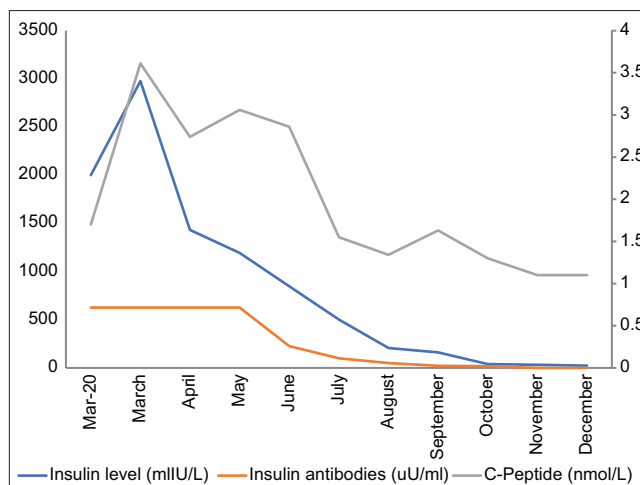


Figure 2: Temporal changes in insulin, insulin antibodies, and C-peptide levels

Management of IAS requires discontinuation of the offending agent, a low-carbohydrate diet, and often the use of glucocorticoids. Acarbose, an α -glucosidase inhibitor, was used to treat reactive hypoglycemia but was minimally effective. In our patient, treatment with glucocorticoids was indicated because of severe hypoglycemia. Prednisone was quite effective in controlling glycemic levels and in reducing IAA titers.

CONCLUSIONS

This is the first case report of IAS in an Emirati patient caused by the use of clopidogrel. IAS should be considered in the differential diagnosis of patients with hyperinsulinemic hypoglycemia. Clinical suspicion of IAS in affected patients can prevent costly imaging and unnecessary surgery.

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Declaration of patient's consent

The authors certify that they have obtained the appropriate patient consent. The patient has given the consent for images and other clinical information to be reported in the journal. The patient understands that no names and initials will be published and all due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Authors' Contribution

All authors were involved in the care of the reported case and the drafting and revising of the manuscript. They all approved the final version of the manuscript.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

No prior ethical approval is required at our institution for single case reports and small case series. However, the patient provided consent for anonymous reporting.

Data availability

Not available

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