INTERNAL MEDICINE

□ CASE REPORT □

Restoration of the Hypothalamic-pituitary-adrenal Response to Hypoglycemia in Type 2 Diabetes by Avoiding Chronic Hypoglycemia

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Abstract

An impaired ability to sense and respond to drug-induced hypoglycemia is a common and serious complication in diabetic patients. The hypothalamic-pituitary-adrenal (HPA) axis activity plays a critical role in the counterregulatory response to hypoglycemia. We herein report a case that experienced restoration of a blunted HPA axis by avoiding hypoglycemia with the use of the DPP-4 inhibitor sitagliptin.

Key words: hypoglycemia, insulin, DPP-4 inhibitor, hypothalamic-pituitary-adrenal

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Case Report

A 69-year-old woman was diagnosed with diabetic retinopathy at 64 years of age, and diabetes medical treatment was thus initiated. She had bilateral proliferative diabetic retinopathy and underwent laser photocoagulation. Upon treatment with biphasic insulin Novolin 30R® 7-0-3 unit dose, the HbA1c levels were 5.5%. She had frequently experienced symptomatic hypoglycemia, such as cold sweating and palpitation. Her hypoglycemia was also confirmed by self-monitoring of blood glucose. On the day of admission, the patient had injected herself with 45 units of insulin Novolin 30R in an attempted suicide. The ambulance worker found that she was comatose and had capillary glucose levels of <20 mg/dL. After the administration of a 50 mL intravenous bolus of 50% glucose, a continuous infusion of 10% glucose was administered in the hospital; she experienced intermittent hypoglycemia over the course of 24 h.

Her height/weight was 140 cm and 44.35 kg, respectively. Her physical exam was unremarkable. She had no apparent renal or hepatic dysfunction. The endocrine test results at early morning on the day after admission displayed adrenocorticotropic hormone (ACTH) 4.7 pg/mL, cortisol 8.1 μg/dL, and insulin-like growth factor (IGF)-1 70 ng/mL. Her 24-hour urinary-free cortisol levels were 10.7 μg/day. The basal serum prolactin (PRL), thyroid, and gonadotropin levels were normal. Circadian variations in plasma ACTH and cortisol were lost.

To evaluate the hypothalamic-pituitary-adrenal (HPA) function, a corticotropin-releasing hormone (CRH) stimulation test and insulin tolerance test (ITT) was performed (Figure A). The patient had a normal response to the CRH test (100 μg), with plasma ACTH levels of 36.3, 143.0, 110.0, 71.1, and 51.1 pg/mL at 0, 30, 60, 90, and 120 min, respectively. The ITT (intravenous 0.11 unit/kg insulin) revealed a normal response of GH; a blunted response of plasma ACTH and cortisol, even though the serum glucose levels in response to ITT achieved insufficient levels, 53 mg/dL. There was no abnormality in the pituitary gland on MRI. The pituitary reactions in the gonadotropin-releasing hormone (GRH), thyrotropin-releasing hormone (TRH), and luteinizing hormone-releasing hormone (LH-RH) loading tests were normal. The patient displayed low levels of spon-

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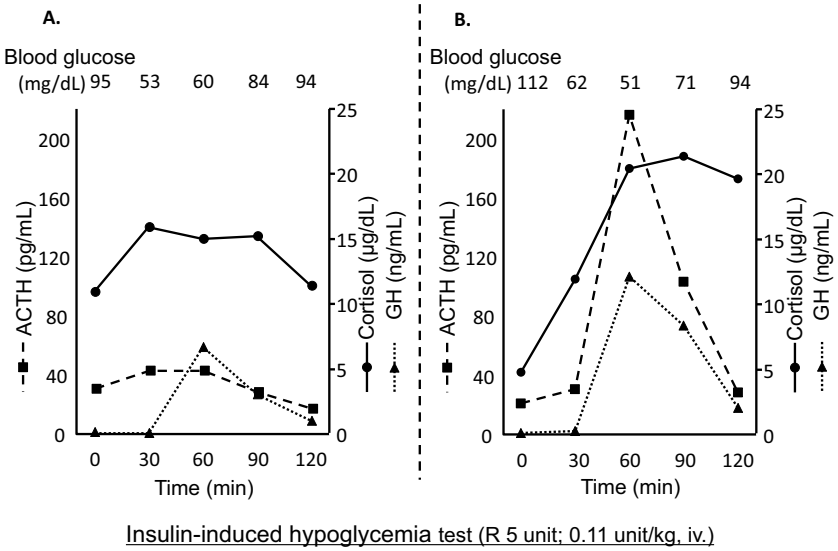

Figure. **Insulin tolerance test. A: Evaluation at admission, B: Evaluation at 8 months after the subcutaneous insulin treatment was terminated and sitagliptin treatment (50 mg/day) was initiated.**

taneous and stimulated cortisol secretion, particularly in reaction to hypoglycemia.

Dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin (50 mg/day)) treatment was initiated in the replacement of subcutaneous insulin treatment. During the 8-month follow-up, the patient maintained a good control of her blood sugar levels (HbA1c 6.9%). The HPA axis was then re-evaluated. Her 24-hour urinary-free cortisol levels were 18.2 μg/day. We observed a clear amelioration in the ACTH and cortisol serum responses to the ITT (Figure B).

Chronic hypoglycemia has been shown to induce HPA deficiency (1-3); however, the duration and magnitude of hypoglycemia that results in HPA deficiency have not been experimentally revealed. In our case, sitagliptin treatment for 8 months might have restored blunted HPA. However, there were significant limitations associated with this study. First, our ITT procedure reached insufficient levels of plasma glucose to evaluate HPA. We considered another test to utilize a higher dose of insulin to test HPA deficiency; however, it was not possible because the patient experienced palpitation during both ITT procedures and also feared undergoing a high degree of hypoglycemia due to her past experiences of frequent severe hypoglycemia attacks. Second, the urine free cortisol excretion level improved to within the normal range; however, the magnitude of recovery in cortisol levels was not remarkable. In this regard, we expected that a much longer follow-up without hypoglycemia might improve a greater improvement in the levels of cortisol. Unfortunately, this patient now receives care at another clinic. Therefore, we could not follow up her clinical course.

Deficiency in HPA may be associated with a compromised psychophysiological response, including food intake against hypoglycemia stress (4, 5). We emphasize that the avoidance of chronic hypoglycemia sensitizes patients to HPA axis activity as a counter response to hypoglycemia. Clinicians should be aware that avoiding iatrogenic hypoglycemia is essential for successful diabetic therapy.

Author's disclosure of potential Conflicts of Interest (COI).
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