

[CASE REPORT]

Glucose-responsive Insulinoma with Insulin Hypersecretion Suppressed by Metformin

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Abstract:

In type 2 diabetes mellitus, metformin suppresses excessive insulin secretion in relation to the intake of glucose. We herein report the case of a 45-year-old man with glucose-responsive insulinoma whose responsive hypoglycemia was alleviated by metformin. The patient had a history of a postprandial loss of consciousness, resulting in hospital admission. He refused surgery and diazoxide administration. A 75-g oral glucose tolerance test after metformin administration revealed the suppression of glucose-responsive insulin hypersecretion and responsive hypoglycemia. Pancreatic head duodenectomy was performed, which alleviated the symptoms. Metformin administration in patients with glucose-responsive insulinoma may therefore be effective for preventing responsive hypoglycemia and hyperinsulinemia.

Key words: insulinoma, metformin, responsive hypoglycemia, postprandial, case report

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Introduction

Insulinomas are rare pancreatic tumors, with an estimated incidence of 4 per 1,000,000 person-years (1), that cause autonomous insulin secretion, leading to hypoglycemia. Historically, fasting hypoglycemia has been considered the primary presenting feature of insulinoma. However, some patients with insulinoma have an excessive response to glucose-loading. Occasionally, hypoglycemic symptoms are not apparent in the early-morning fasting state, instead appearing postprandially. Glucose-responsive insulinomas with insulin hypersecretion are relatively rare, but some cases have been reported. A recent retrospective review from the Mayo Clinic showed that a total of 6% of patients with insulinoma presented only with postprandial-related symptoms (2). In many such cases, the immune reactive insulin (IRI) peak in the oral glucose tolerance test (OGTT) is higher than in cases of typical insulinomas (3-8).

Radical treatment of insulinoma involves surgical resection, but it is not uncommon for insulinomas to recur or me-

tastasize after surgery. In some patients, drug therapy is required. Octreotide or lanreotide in particular is recommended if somatostatin receptor imaging is positive and/or hormonal symptoms are present. Everolimus and cytotoxic chemotherapy are also recommended treatment options for cases with progressive and/or metastatic insulinoma (9). Diazoxide, which suppresses insulin secretion directly, is administered to prevent insulinoma-related hypoglycemia. However, adverse effects necessitate discontinuation of treatment in some patients.

Responsive hypoglycemia has been reported in patients with idiopathic hypoglycemia due to an abnormal increase in insulin sensitivity (10) and in those with early-stage type 2 diabetes mellitus developing postprandial insulin hypersecretion or delayed insulin secretion in association with increased insulin resistance (11). Metformin alleviates insulin resistance and suppresses insulin hypersecretion. It is therefore effective for preventing postprandial responsive hypoglycemia. However, there have been no case reports of insulinomas presenting with postprandial hypoglycemia in which metformin was administered to prevent hypoglycemia.

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Table 1. Laboratory Test Findings at Admission, Year X.

Complete Blood Count	
White blood cell	6,740 / μ L
Red blood cell	447 $\times 10^4$ / μ L
Hemoglobin	11.2 g/dL
Platelet	27.2 $\times 10^4$ / μ L
Blood chemistry	
Total protein	6.5 g/dL
Albumin	3.9 g/dL
Aspartate aminotransferase	15 IU/L
Alanine aminotransferase	15 IU/L
Lactate dehydrogenase	169 IU/L
Alkaline phosphatase	228 IU/L
γ -glutamyltransferase	18 IU/L
Total bilirubin	0.7 mg/dL
Blood urea nitrogen	12.8 mg/dL
Creatinine	0.7 mg/dL
Sodium	141 mEq/L
Potassium	3.8 mEq/L
Chloride	108 mEq/L
Calcium	9.2 mg/dL
Phosphorus	3.8 mg/dL
LDL-Cholesterol	114 mg/dL
HDL-Cholesterol	52 mg/dL
Triglyceride	39 mg/dL
Fasting plasma glucose	42 mg/dL
Hemoglobin A1c	4.4 %
Insulin antibody	<0.4 %
Endocrinology	
Adrenocorticotrophic hormone	22 pg/mL
Cortisol	11.3 μ g/dL
Thyroid stimulating hormone	1.92 μ IU/mL
Free triiodothyronine	3.19 pg/mL
Free thyroxine	1.06 ng/dL
Growth hormone	0.17 ng/mL
Insulin-like growth factor-I	136 ng/mL
Prolactin	22.98 ng/mL
Intact parathyroid hormone	41 pg/mL
Glucagon	158 pg/mL
Gastrin	140 pg/mL
Immune reactive insulin	7.2 μ IU/mL
C-peptide immunoreactivity	1.37 ng/mL

We herein report the outcomes of metformin administration in a 45-year-old man with a glucose-responsive insulinoma.

Case Report

A 45-year-old man reported cold sweats, dizziness, and clouded vision 1 to 2 hours after consuming non-alcoholic carbonated drinks over the past 15 years, although he had not visited a hospital for these symptoms. A year earlier, he had lost consciousness while driving 1 hour after consuming a non-alcoholic carbonated drink and was admitted to the emergency department of a hospital. He had no significant

Table 2. Fasting Glucagon-loading Test Results at Admission, Year X.

	0 min	6 min	30 min
PG (mg/dL)	39	69	87
IRI (μ IU/mL)	11.5	62.1	761.9
CPR (ng/mL)	2.2	5.28	26.07

PG: plasma glucose, CPR: C-peptide immunoreactivity, IRI: immune reactive insulin

family history.

A diagnosis of glucose-responsive insulinoma was made but the patient refused extended hospitalization for detailed tests or surgery, due to his work situation. Therefore, his condition was monitored on an outpatient basis. The administration of diazoxide 50 mg 3 times a day was initiated, and after a week, the dosage was increased to 75 mg 3 times a day. He was unable to visit the hospital regularly because diazoxide was quite expensive for him and he was very busy at work. Three months after the start of oral administration, the patient himself discontinued his therapy, stating that the drug did not seem to have any effect. One year after this first hospitalization, he lost consciousness while driving once again, approximately 1 hour after eating lunch, resulting in a single-vehicle accident. He was therefore hospitalized again.

At this second hospitalization, the patient's height was 171 cm, his body weight was 71.5 kg, and his body mass index was 24.6 kg/m². Hematology tests showed low fasting plasma glucose and hemoglobin A1c levels (Table 1), and the fasting glucagon-loading test was positive (Table 2). Abdominal computed tomography (CT) did not show a tumor, but abdominal magnetic resonance imaging (MRI) revealed a densely stained, poorly perfused area in the pancreatic uncus. Endoscopic ultrasound (EUS) showed a hypoechoic area measuring 19 \times 14 mm in the pancreatic uncus, and somatostatin scintigraphy showed a nodule measuring approximately 2 cm in diameter in the pancreatic uncus (Fig. 1). A cervical ultrasound was normal and did not show enlargement of the parathyroid glands. The selective arterial calcium injection test (SACI) showed increased IRI in the dorsal pancreatic artery (Fig. 2). Therefore, pancreatoduodenectomy was performed, and the lesion thought to be responsible for the patient's condition, a nodule in the pancreatic uncus, was excised. The excised nodule was an insulinoma that showed positive insulin immunostaining findings and had a Ki-67 index level below 1% according to the pathological status (Fig. 3). After the surgery, the patient's symptoms were alleviated and have not recurred since.

A 75-g OGTT was performed before and after surgery, with and without metformin administration, to evaluate the efficacy of metformin for suppressing responsive hypoglycemia associated with glucose-responsive insulinoma. A 75-g OGTT had been performed at the time of the initial diagnosis (Year X-1), immediately before surgery (Year X), and 18 months post-surgery (Year X+1.5), in Years X and Year X+

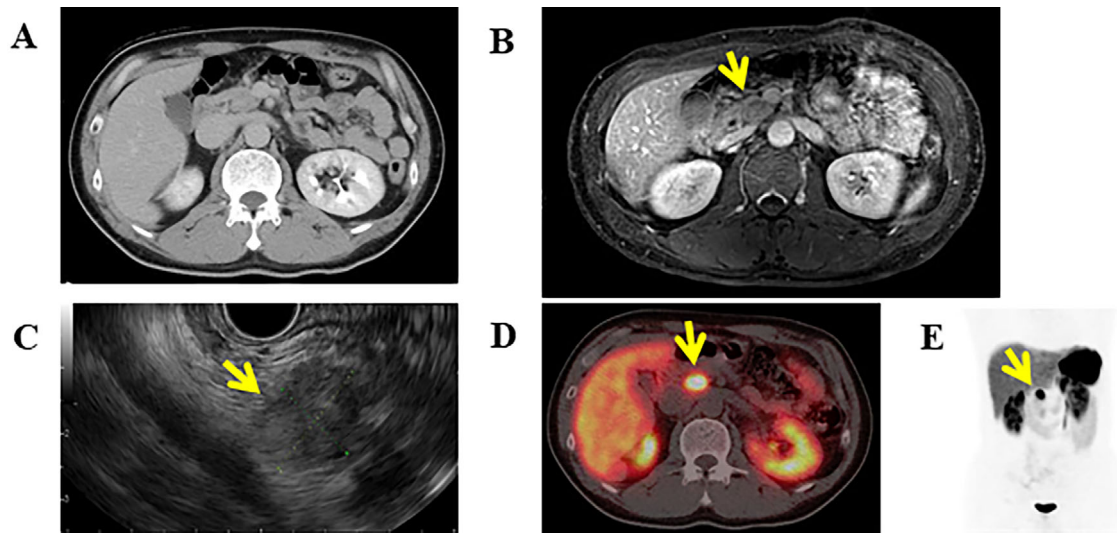


Figure 1. Imaging findings. A: Abdominal computed tomography (CT) did not show a tumor. B: Abdominal magnetic resonance imaging (MRI) revealed a densely stained, poorly perfused area in the pancreatic uncus (arrow). C: Endoscopic ultrasound (EUS) showed a hypochoic area measuring 19×14 mm in the pancreatic uncus (arrow). D: Somatostatin scintigraphy revealed a tumor measuring approximately 2 cm in diameter in the pancreatic uncus (arrow). E: Somatostatin scintigraphy of whole-body planar images showed an uptake in the pancreas (arrow).

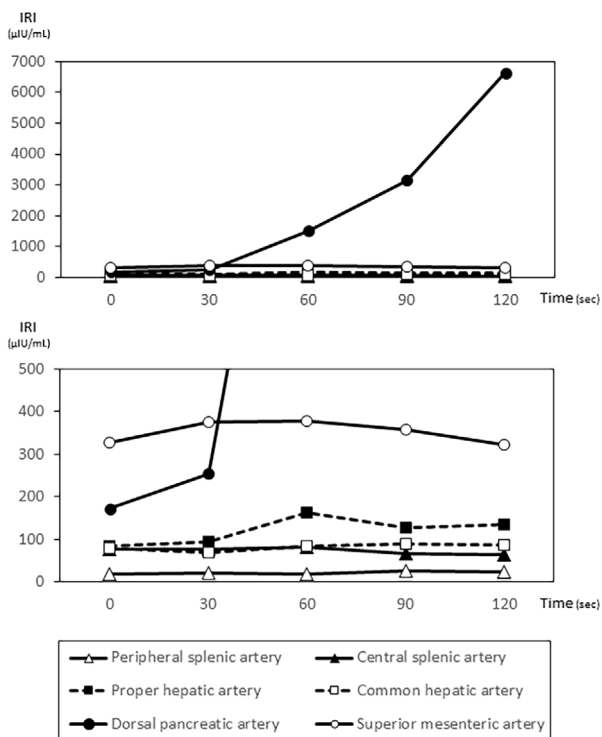


Figure 2. Selective arterial calcium injection (SACI) test results at admission, Year X.

1.5, the 75-g OGTT was conducted with and without metformin (on different days). Metformin (500 and 750 mg in Years X and X+1.5, respectively) was administered 30 minutes before test initiation. The patient provided his written informed consent for the tests. All procedures followed were in accordance with the Declaration of Helsinki.

In Year X - 1, the 75-g OGTT showed insulin hypersecretion, followed by hypoglycemia 2 hours later. In Year X, the test showed an even higher level of insulin hypersecretion, followed by hypoglycemia 1 hour later. Metformin administration suppressed insulin hypersecretion in a dose-dependent fashion and also suppressed responsive hypoglycemia. In Year X+1.5, the 75-g OGTT suppressed insulin hypersecretion in comparison to the test results pre-surgery. The administration of 750 mg metformin decreased the height of the insulin concentration peak and delayed the time of the peak from 30 to 60 minutes (Fig. 4).

Discussion

The findings of the present case report suggest that metformin administration to patients with glucose-responsive insulinomas is effective for preventing responsive hyperinsulinemia and the resulting responsive hypoglycemia.

Insulinomas often involve deficient glucose responsiveness with autonomous insulin secretion, independent of the patient's blood glucose concentration. However, the insulinoma in this case was glucose-responsive. The glucokinase activity defines glucose responsiveness in pancreatic β -cells. However, irrespective of glucokinase expression, some insulinoma cell lines are glucose-responsive, whereas others are not (12). Therefore, the abnormal response of glucokinase may be involved in the development of glucose-responsive insulinomas.

Another reason why some insulinomas respond to glucose stimulation may be related to the expression of receptors on β -cells. In insulinoma cells, the calcium-sensing receptor (CaSR) expression is increased, which is why SACI is use-

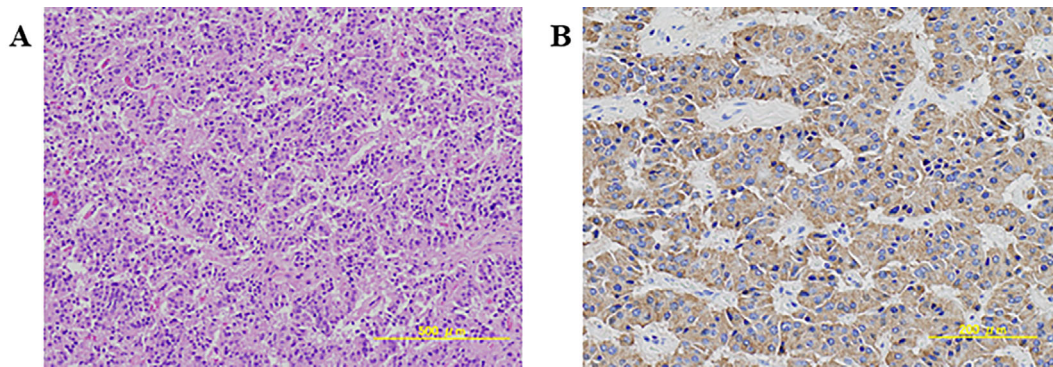


Figure 3. A microscopic examination of the resected tumor. A: Hematoxylin and Eosin staining section of the tumor (magnification, $\times 100$). B: Immunohistochemical staining for insulin (magnification, $\times 200$).

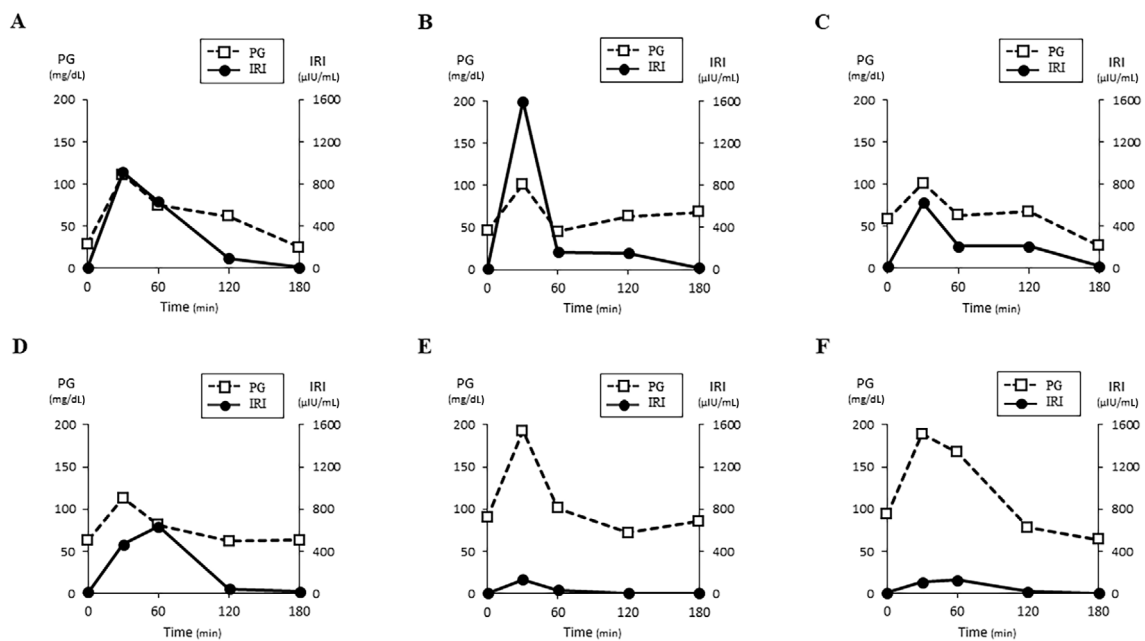


Figure 4. Results of the 75-g oral glucose tolerance test (OGTT) in Year X-1. PG: plasma glucose, IRI: immune reactive insulin, A: In year X-1, No metformin administration. B: In year X, No metformin administration. C: In year X, Administration of metformin 500 mg. D: In year X, Administration of metformin 750 mg. E: In year X+1.5, No metformin administration. F: In year X+1.5, Administration of metformin 750 mg.

ful for the diagnosis. In SACI, the increased calcium ion concentration in insulinoma cells activates the CaSR, resulting in insulin secretion. Therefore, insulinomas have a high affinity for calcium. It is now generally accepted that the glucose-sensing machinery and insulin secretion of β -cells depend on glucose metabolism (13). In recent years, the insulin secretion mechanism of the glucose-sensing receptor (GSR) has been reported (14), being said to be related to glucose metabolism (15). The GSR molecular entity is a T1 R3-CaSR heterodimer that responds to glucose as well as calcium, and its glucose sensitivity is very high (16). In typical insulinoma cells, the CaSR may be expressed at a higher level than the GSR; it is therefore possible that glucose responsiveness is depressed.

In addition, the abnormal expression of glucose transporters by pancreatic β -cells has been suggested as being involved in the characteristic glucose responsiveness associated with insulinomas. Normal pancreatic β -cells express low levels of glucose transporter (GLUT) 1, which is a low-K_m glucose transporter protein, and high levels of Glut 2, which is a high-K_m glucose transporter protein. Surgically excised insulinoma specimens, however, have been reported to show high levels of Glut 1 and low levels of Glut 2 (17, 18). This suggests that glucose responsiveness may change based on alterations in the ratio of Glut 1 to Glut 2 in insulinomas. However, the mechanism underlying the reduced glucose responsiveness in insulinomas remains unclear, and further research is needed. Comparisons with glucose-responsive insu-

linomas may hold the key to elucidating this mechanism.

Metformin is the traditional drug used in the treatment of type 2 diabetes mellitus. Its principal mechanisms of action are the suppression of gluconeogenesis in the liver and promotion of the uptake of glucose by the skeletal muscles and fatty tissues (19). In the patient described in this report, metformin administration resulted in the suppression of insulin secretion. Given the known medicinal effects of metformin, the suppression of insulin secretion may be caused by mechanisms associated with the suppression of glucose absorption in the small intestine (20) and the alleviation of insulin resistance. Another possible mechanism may be that metformin acts on pancreatic β -cells directly and suppresses insulin secretion. The effects of metformin in the liver are elicited via a decrease in adenosine triphosphate (ATP) concentration due to organic cation transporter 1 (OCT-1)-mediated inhibition of the mitochondrial respiratory chain complex I in hepatocytes, thereby resulting in AMP-activated protein kinase (AMPK) (21). Similarly, in pancreatic β -cells, if metformin reduces the ATP concentration and activates AMPK, mediated by the mitochondria, insulin secretion is inhibited. There have been reports of the inhibition of AMPK activation and suppression of insulin secretion in pancreatic β -cells (22, 23). It is therefore possible that metformin has a direct effect on β -cells.

Diazoxide acts on the ATP-sensitive potassium channels (K_{ATP} channels) of pancreatic β -cells, suppressing insulin secretion; it is therefore widely used to prevent insulinoma-related hypoglycemia (24). However, it can induce various adverse effects, including nausea, edema, congestive heart failure, alopecia, hyperglycemia, and ketoacidosis. In the present case, the patient was unable to continue diazoxide treatment, likely because diazoxide had excessive effects when administered in the fasting state and insufficient effects when administered postprandially. In addition, adverse effects of diazoxide may have occurred. Although metformin can also cause adverse effects, such as gastrointestinal symptoms that occur readily at high doses and lactic acidosis that occurs occasionally, it is a very safe drug that is widely used as the first-line treatment for type 2 diabetes mellitus worldwide (25). It has been suggested that metformin may reduce hypoglycemia in cases of glucose responsive insulinoma, indicating the possibility that metformin could be substituted for diazoxide. The mechanisms underlying the functional secretion of glucose-responsive insulinoma and the suppression of insulin secretion by metformin remain unclear and require further investigations.

In summary, metformin administration in patients with glucose-responsive insulinoma may be effective for preventing responsive hypoglycemia. Our findings also suggest that postoperative monitoring based on the insulin secretion response in the 75-g OGTT is useful for ensuring good outcomes.

The authors state that they have no Conflict of Interest (COI).

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