# Diagnosis and Treatment Course of Insulinoma Presenting as Hypoglycemia Unawareness Using a Factory-Calibrated Continuous Glucose Monitoring System

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: **Male, 35-year-old**
Final Diagnosis: **Insulinoma**
Symptoms: **Loss of consciousness**
Medication: **—**
Clinical Procedure: **—**
Specialty: **Endocrinology and Metabolic • Metabolic Disorders and Diabetics**

Objective: **Rare disease**

Background: Insulinoma presenting only with postprandial hypoglycemia is difficult to diagnose. Repeated episodes of hypoglycemia can lead to "hypoglycemia unawareness", which can be even more dangerous and requires early detection and treatment.

Case Report: We report the case of a 35-year-old man with an insulinoma presenting as postprandial hypoglycemia who was treated with diazoxide and monitored using a factory-calibrated continuous glucose monitoring (CGM) system until surgery. When the patient initially presented with hypoglycemia, relative hyperinsulinemia was present. There were no obvious abnormal findings on imaging examination. Hypoglycemia was not repeated on endocrinological examination, even while fasting. Four months later, asymptomatic postprandial hypoglycemia of 48 mg/dL was incidentally detected. Although none of the conventional 3 indicators of relative hyperinsulinemia were met, an insulinoma was suspected based on the results of a fasting test. Computed tomography and magnetic resonance imaging showed a mass in the pancreatic uncinate process, and selective intra-arterial calcium infusion revealed high insulin levels in the same area, leading to a diagnosis of insulinoma. The patient was treated medically with diazoxide, using a factory-calibrated CGM system until surgery. Subsequently, pancreatic mass enucleation was performed, and pathological examination confirmed the diagnosis. After surgery, the hypoglycemia resolved, and the blood glucose level remained within a range of 100 to 180 mg/dL, without the use of diazoxide.

Conclusions: A factory-calibrated CGM system is useful for evaluating the course of medical treatment, monitoring hypoglycemic episodes during the diagnostic period, detecting unconscious hypoglycemia, monitoring the response to medical treatment, and treating insulinoma after surgery.

Keywords: **Insulinoma • Hypoglycemia • Diazoxide**

Abbreviations: **CGM** – continuous glucose monitoring; **ISFG** – interstitial fluid glucose; **BG** – blood glucose level; **IRI** – immunoreactive insulin; **MRI** – magnetic resonance imaging

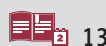Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936723
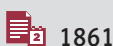
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# Background

Approximately 90% to 95% of insulinomas are benign tumors, and the 5-year survival rate after resection is expected to be 95% to 100% [1]. Large series in the past have reported recurrence in 3.0% to 5.4% of cases [2]. Differentiation between benign and malignant tumors can be difficult and is based on a combination of preoperative and intraoperative findings [1]. Histopathological markers that are associated with the prognosis of insulinoma include the Ki-67 growth index, tumor size, vascular invasion, and local invasion [3]. The treatment of insulinoma is mainly surgical, but surgery should be performed only once a diagnosis has been confirmed; a blind pancreatectomy is not an appropriate treatment at this time. In addition, drugs such as somatostatin analogs and diazoxide that inhibit the biosynthesis and release of insulin can be used in cases in which a lesion cannot be identified after various imaging tests or when surgical treatment is difficult because of financial circumstances.

The continuous glucose monitoring (CGM) system was first certified by the US Food and Drug Administration in 1999 and has benefited many people with diabetes over the past 2 decades, as considerable technological advances have led to regulatory approvals for multiple continuous and semi-continuous blood glucose (BG) monitors [4]; CGM is also reportedly useful for determining the presence of hypoglycemia and for the application of drug therapy in patients with insulinoma [5]. The glucose is measured in the interstitial fluid glucose (ISFG) throughout the day using the glucose oxidase reaction via fluorescence or intravenously via mid-infrared, fluorescence, electrochemical, or electrochemical impedance spectroscopy. Then, it is converted to a BG concentration through a calibration process using a user's frequent self-monitoring of BG levels [4]. The Freestyle Libre (Abbot Diabetes Care, Oxon, UK), a factory-calibrated CGM system, is the first glucose monitoring device that does not require calibration, with the added benefit of similar performance in both accuracy and BG control of CGM devices that require calibration at least twice a day [6]. CGM measures the glucose concentration in ISFG throughout the day and is widely used to manage BG levels in patients with diabetes mellitus; it is also reportedly useful for determining the presence of hypoglycemia and the application of drug therapy in patients with insulinoma. Except for some devices utilizing real-time CGM systems, however, most currently available CGM systems require frequent self-measurements and the calibration of capillary BG levels, limiting monitoring to the retrospective identification of past hypoglycemic events. Several devices have been developed to measure the glucose concentration in ISFG. For example, the Abbott FreeStyle Libre Pro (Abbot Diabetes Care), a factory-calibrated CGM system intended for professional use only, can monitor the ISFG for 14 consecutive days per sensor, longer than other devices.

Here, we report a patient with an insulinoma in the pancreatic uncinate process who was treated using diazoxide and an Abbott FreeStyle Libre Pro factory-calibrated CGM system until surgery.

# Case Report

A 35-year-old man started experiencing dizziness while running marathons at the age of 33 years and stopped running marathons at the age of 34 years. In the evening after dinner, while stretching after muscle training, he became unconscious and was rushed to our hospital (at the age of 35 years). His BG level was 20 mg/dL, and the disturbance of consciousness was quickly improved by the intravenous administration of glucose. An endocrinological examination and a computed tomography (CT) scan of his entire body, including his head, were performed, but no obvious abnormal findings were found. Blood samples taken at 4 a.m. on the day after admission showed a fasting BG level of 68 mg/dL and a serum insulin level of 8.9 μU/mL, which was considered to be high relative to the BG level, and insulin overproduction was suspected. However, hypoglycemia was not observed during the hospital stay even while he was fasting, and hypoglycemia arising from heavy alcohol consumption was considered to be the cause. He was subsequently discharged from the hospital. Four months later, an asymptomatic postprandial hypoglycemia level of 48 mg/dL was incidentally detected during a close examination for high γGTP levels, and the patient was hospitalized once again. His family history was unremarkable, with no evidence of any endocrine disorders. He had no significant physical examination findings (body mass index, 21.9 kg/m$^2$).

## Investigation

Laboratory test results revealed an HbA1c of 4.4% (28 mmol/mol), fasting BG level of 68 mg/dL, and a high fasting insulin level of 8.9 μU/mL, despite hypoglycemia. His insulin antagonist hormone levels (ACTH, 12.07 pg/mL; cortisol, 2.6 μg/dL; TSH 4.09 μIU/mL; FT4 1.23 ng/dL) were in the reference range, and the anti-insulin antibody test result was negative. The results of liver function tests were an AST/ALT of 38/55 IU/L and a γGTP of 84 U/L, and his kidney function test results were in the reference range. The endocrinological and imaging tests ruled out multiple endocrine neoplasia type 1 (intact PTH, 45 pg/mL; calcium, 9.2 mg/dL; phosphorus 2.9 mg/dL; GH, 1.74 ng/mL; IGF-1, 182 ng/mL), adrenal insufficiency, and hypothyroidism. None of the 3 indicators (ie, the Fajans index, Grunt index, or Turner index) for relative hyperinsulinemia were met, but the Endocrine Society index (BG <55 mg/dL; immunoreactive insulin [IRI] ≥3 μU/mL) was met, and a fasting test was performed. After 11 h of fasting, the test results continued to show a BG level of below 55 mg/dL,

**Figure 1.** Abdominal diffusion-weighted magnetic resonance imaging showed relatively strong enhancement effect from the early phase at the pancreatic uncinate process.

and at 19 h, the BG level was 50 mg/dL, so the fasting test was terminated. At that time, the plasma IRI level was 4 µU/mL and the C peptide level was 0.6 ng/mL. Since an insulinoma was suspected, an abdominal CT examination was performed and a suspected mass lesion (22×15 mm) was newly identified in the pancreatic uncinate process, with enhancement that was approximately equal to that of the pancreatic parenchyma. Although this lesion was not visible on the magnetic resonance imaging (MRI) findings that had been obtained
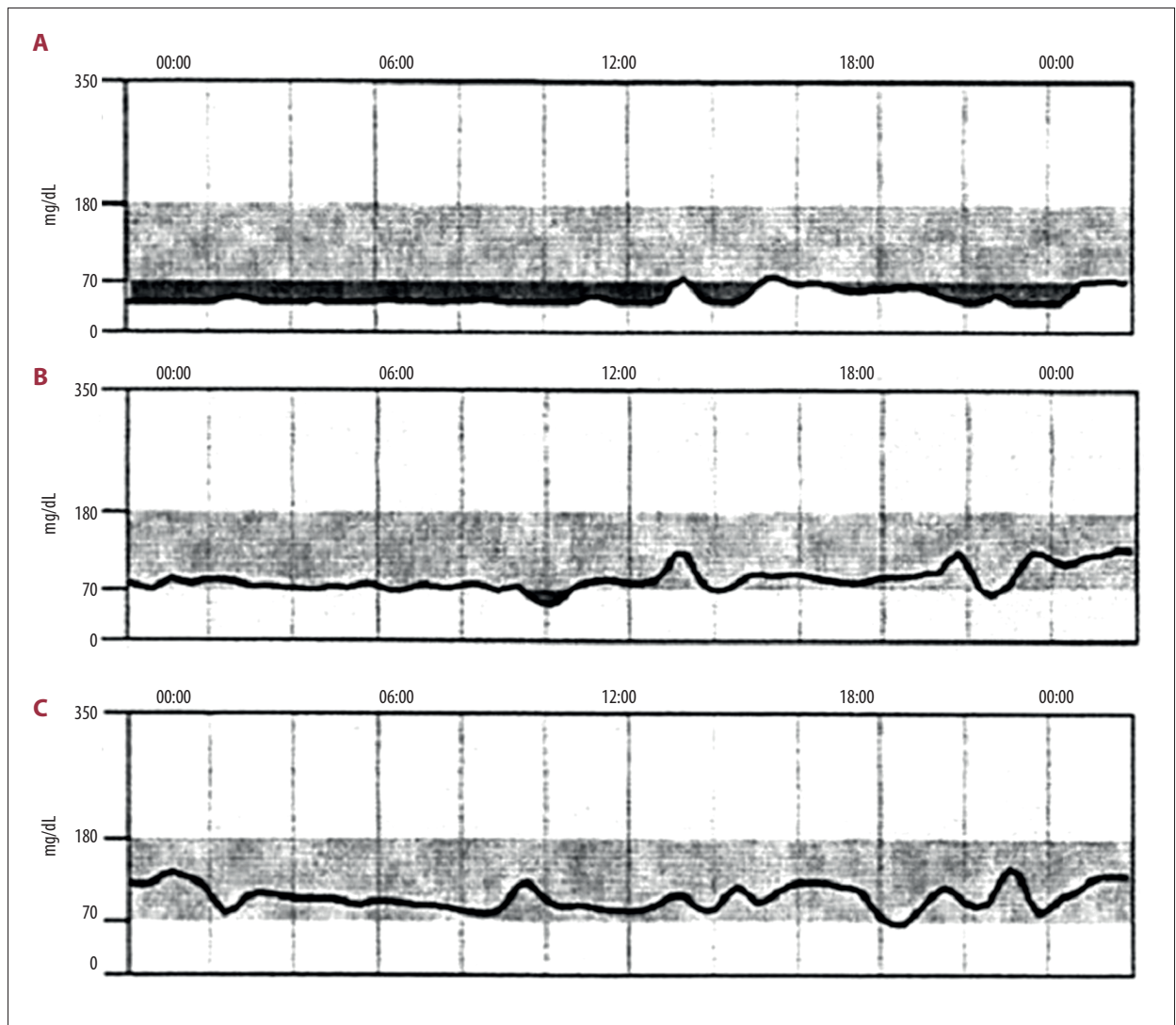


**Figure 2.** Results of Freestyle Libre Pro continuous glucose monitoring before and after diazoxide administration. (**A**) Before, (**B**) 2 days after, and (**C**) 4 days after. Before starting diazoxide, hypoglycemia appeared throughout the day. Diazoxide was started at 75 mg/day (1.05 mg/kg), with mild improvement and no observed adverse effects.
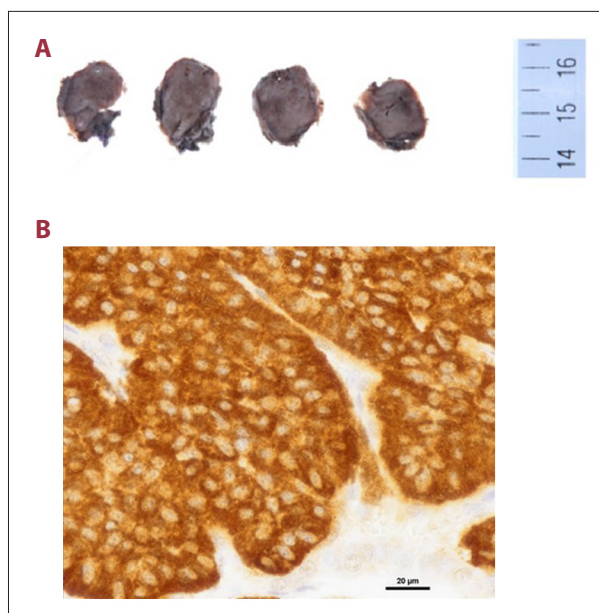
**Figure 3.** Histological and immunohistological findings of tumors in the pancreatic uncinate process. (**A**) Surgical specimen of pancreas: gross classification was nodule type, and tumor diameter was 19×17×16 mm. (**B**) Histopathology: pancreatic tumor cells with Ki-67 percentage of 3% of synaptophysin (synaptophysin staining, ×200).

1 month earlier, a subsequent MRI of the abdomen showed a low signal during T1, a faint high signal during T2, and a high signal during diffusion-weighted MRI in the same region, indicating a relatively strong enhancement effect from the early phase (**Figure 1**). Selective intra-arterial calcium injections showed a significant increase in IRI only in the common duct of the inferior pancreaticoduodenal artery and the first jejunal artery. Hypoglycemia was observed throughout the day using the factory-calibrated CGM system, with a 24-h BG range of 45 to 61 mg/dL. No hypoglycemic symptoms were observed after selective intra-arterial calcium injections, even when the BG levels were between 45 and 61 mg/dL.

**Treatment**

The decision was made to treat the patient medically until surgery. After starting diazoxide at a dosage of 75 mg/day (1.05 mg/kg); the hypoglycemia improved (**Figure 2**), and no adverse effects were observed. The patient subsequently underwent a laparoscopic pancreatic tumor (19×17×16 mm) enucleation.

A pathological examination revealed a well-differentiated neuroendocrine grade 2 tumor with a Ki-67 percentage of 3% (**Figure 3**). The hypoglycemic periods resolved after the surgery without the continued use of diazoxide.

**Outcome and Follow-Up**

At the 1-month postoperative follow-up, the range of BG levels was 80 to 182 mg/dL, and there were no episodes of hypoglycemia after an overnight fast. We monitored his glucose levels every month for 6 months, and then every 6 months thereafter as an outpatient, and he had not developed any hypoglycemia, even after exercising, and his weight had not changed significantly.

**Discussion**

Several reports have described the use of CGM during the diagnosis and resection of insulinoma [7]. In the present case, we successfully avoided hypoglycemia in a patient with insulinoma with postprandial hypoglycemia by monitoring his ISFG levels using the Abbott FreeStyle Libre Pro, a factory-calibrated CGM system, before and after treatment with diazoxide. The factory-calibrated CGM was useful for determining the treatment efficacy of diazoxide therapy and for dose adjustments, and its future use for such purposes is expected. Since delays in responding to central nervous system symptoms caused by hypoglycemia can lead to brain damage and even death, managing patients in a timely and safe manner is crucial once an insulinoma is suspected; in reality, however, delays in the detection and diagnosis of insulinomas are common. In terms of detection, more than 80% of patients with insulinoma present with fasting hypoglycemia, which makes a diagnosis difficult in patients who present with only postprandial hypoglycemia [8], as in our case. Furthermore, repeated episodes of hypoglycemia can lead to "hypoglycemia unawareness", which prevents early measures from being taken to prevent any worsening of the hypoglycemia and makes it harder to detect.

Confirming the presence of hypoglycemia arising from an insulinoma is often difficult [9]. In terms of the time required to obtain a diagnosis, as many as 50% of patients are diagnosed 5 years after the onset of symptoms [10], and about 20% are misdiagnosed as neurological or psychiatric disorders until the time of insulinoma diagnosis [8]. The classical diagnosis of insulinoma is based on meeting the criteria of Whipple's triad: central nervous system symptoms during fasting, a plasma glucose (PG) level <50 mg/dL at the onset of symptoms, and the relief of symptoms with glucose administration. There are also 3 assessments of insulin hypersecretion during fasting: the Fajans index (IRI/PG), the Grunt index (PG/IRI), and the Turner index (IRI×100/[PG-30]). However, none of these 3 indices, or other imaging modalities, such as angiography and dynamic CT, are sufficiently sensitive for the diagnosis of insulinoma [9]. Image processing techniques are often unable to detect a significant percentage of insulinomas (CT, 55%; MRI, 42%) [8] because of the characteristics

of insulinoma: 81.1% of cases are less than 2 cm in size, the metastasis rate is 6.6%, and 12.6% of cases have multiple lesions [11]. In adults with symptoms of neuroglycopenia and confirmed hypoglycemia, the criterion standard for biochemical diagnosis is the measurement of PG, insulin, C peptide, and proinsulin levels during a 72-h fasting period; according to Service et al [12], up to 99% of insulinomas can be detected using this prolonged fasting test. Of note, however, the absolute insulin level does not necessarily increase in all patients with insulinoma; therefore, even normal insulin levels do not rule out the disease [3].

Over the past decade, CGM manufacturers have devoted much effort to overcoming the problem of inadequate accuracy and inconvenience for users [6]. Although the reading by the Abbott FreeStyle Libre Pro we used is highly accurate without calibration, and the operation is user-friendly, it does not have an alarming function for the out-of-range glucose values [13]. On the other hand, other recent monitoring systems, including the Abbott Freestyle Libre and Dexcom G6, are equipped with such a function and are capable of wireless communication [6].

## Conclusions

In summary, we report a case of insulinoma with hypoglycemia unawareness in which appropriate treatment was facilitated using a factory-calibrated CGM system. This system is useful in patients with insulinoma for the detection of hypoglycemia and hypoglycemia unawareness and for monitoring the response to medical treatment, as well as for confirming a complete cure after surgery.

### Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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