Insulinoma Presenting with Reactive Hypoglycemia: Evaluating the Effect of Tumor Resection via Continuous Glucose Monitoring

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Abstract:
A 71-year-old woman previously diagnosed with reactive hypoglycemia was transferred to our emergency unit because of loss of consciousness. Her plasma glucose level was 27 mg/dL, and continuous glucose monitoring (CGM) revealed postprandial asymptomatic hypoglycemia. A hypervascular tumor was identified via computed tomography in the distal pancreas, and the diagnosis of insulinoma was confirmed using the selective arterial calcium stimulation test. Although no episodes of hypoglycemia were observed during CGM after resection, a pathological examination identified regional lymph node metastasis. It is important to consider insulinoma as a cause of postprandial hypoglycemia, and CGM is useful for evaluating treatment outcomes.

Key words: insulinoma, postprandial hypoglycemia, continuous glucose monitoring, metastasis

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Introduction
Insulinoma is a rare tumor of the pancreas, with an annual incidence of 4 per 1 million population per year (1). Since more than 80% of patients with insulinoma demonstrate fasting hypoglycemia (2), it is difficult to distinguish insulinoma from reactive hypoglycemia if patients only have postprandial hypoglycemia. Furthermore, patients with recurrent hypoglycemia may be unaware of the condition, making it more difficult to diagnose the disease (3). There have been some reports of patients with insulinoma wherein continuous glucose monitoring (CGM) was used for a diagnosis (4-6) and throughout the resection process (7, 8). However, there have been no case reports of insulinoma manifesting as postprandial hypoglycemia in which CGM was used throughout the diagnosis, before and after tumor resection. We herein report a case of insulinoma with regional lymph node metastasis in a patient previously diagnosed with reactive hypoglycemia due to the presence of postprandial hypoglycemia. CGM suitably reflected the effects of surgical resection in this case.

Case Report
A 71-year-old woman had struggled for 5 years with frequent episodes of dizziness and anxiety, which usually occurred 1 hour after a meal and were resolved with intake of sugary food. She had neither diabetes nor a history of gastrectomy. Her body mass index was 26.7 kg/m². When she was 66 years old, a 75 g oral glucose tolerance test was performed in a clinic. In this test, her fasting, 2-hour, and 3-hour plasma glucose levels were 83, 89, and 63 mg/dL, respectively (Table 1). Based on rapid and hyper-response of insulin secretion, she was diagnosed with reactive hypoglycemia. She was then given dietetic advice and prescribed miglitol for the treatment of postprandial hypoglycemia.

However, the frequency of the symptoms did not change, and five years after the diagnosis of reactive hypoglycemia, she was transferred to the emergency unit in our hospital because of loss of consciousness. On arrival, her levels of blood glucose, serum insulin, and
In this case, CGM was performed throughout the diagnosis, before and after tumor resection, for a total of 14 days during her hospitalization. Before surgery, her blood glucose levels were 81±16 (mean ± standard deviation) mg/dL and dropped below 70 mg/dL 22 times in 7 days, even with continuous intravenous glucose administration (Fig. 4A). Many of the episodes of hypoglycemia were asymptomatic, and 50% of the total hypoglycemic episodes happened postprandially or after rapid glucose infusion, indicating reactive hypoglycemia on CGM (Fig. 4B). After surgery, CGM revealed blood glucose levels of 123±23 mg/dL and no hypoglycemia (<70 mg/dL), findings that were consistent with a surgical cure of insulinoma (Fig. 4B). These data suggest that CGM is useful for evaluating the treatment outcome of insulinoma. This patient did not complain of further hypoglycemic symptoms during the subsequent six-month follow-up period.

### Discussion

While there have been some reports of insulinoma in which CGM was used for a diagnosis (4-6) and during the resection process (7, 8), our case is the first report of insulinoma presenting with postprandial hypoglycemia in which blood glucose fluctuation was monitored via CGM throughout the diagnosis and management, before and after tumor resection.

Major causes of postprandial hypoglycemia are gastric surgery, reactive hypoglycemia due to hyperinsulinemia in insulin-resistant subjects, and pancreatogenic hypoglycemia,
such as nesidioblastosis (11). Our patient was not obese and did not have a history of diabetes, gastrectomy, or gastric bypass. Furthermore, insulin autoimmune syndrome was excluded, as the serum insulin auto-antibody levels were undetectable. Although the typical symptom of insulinoma is fasting hypoglycemia, a retrospective review indicated that 27% of patients with insulinoma displayed postprandial hypoglycemia (2). Our case illustrates the importance of considering insulinoma as a cause of postprandial hypoglycemia. Very little is known about why some insulinomas cause postprandial hypoglycemia. A previous report noted an increase in the frequency of postprandial hypoglycemia reported in cases of insulinoma over time, from 2% (1987-1992) to 10% (2003-2007) (2). Those data led us to speculate that environmental factors and changes in dietary habits over time might be responsible for the increased frequency of postprandial hypoglycemia. Furthermore, some reports have suggested that diversity of the glucose transporter (Glut) might contribute to the mechanism of postprandial hypoglycemia in insulinoma (12-14). While insulinoma cells usually express Glut-1, original pancreatic β cells normally express Glut-2. However, in patients presenting with postprandial hypoglycemia, the expression of Glut-2 in the tumor cells might increase, leading to excessive insulin secretion after glucose intake (15).

Some patients with insulinoma, including our patient, are unaware of their hypoglycemia as a result of recurrent hypoglycemia. In such cases, CGM is useful for detecting hypoglycemic events, leading to a diagnosis (6, 8). Interestingly, our CGM analysis detected asymptomatic hypoglycemia after meals and even after rapid intravenous glucose infusion. Therefore, intravenous glucose should be administered carefully in patients with insulinoma to prevent reactive hypoglycemia.

Insulinoma is classified as a neuroendocrine tumor by the WHO criteria revised in 2010 (16). In our case, tumor cells were well differentiated, and the cell proliferation rate was low, but regional lymph node metastasis was detected. The incidence of malignant insulinoma is only 5-15% (17), and malignant insulinoma with postprandial hypoglycemia has never been reported. Thus far, the tumor morphology of insulinoma has not been useful for predicting the pattern of hypoglycemia (fasting or postprandial), although the clinical prognosis can be estimated well based on the rate of tumor cell proliferation, evaluated by the mitotic count and Ki-67 staining (18, 19). In addition, tumor size may affect the magnitude of insulin secretion (20). Although the distant metastasis lesion was not detected by CT scan or SRS in the present case, follow-up examinations are important for detecting or ruling-out tumor recurrence, since the clinical course of well-differentiated insulinoma with a metastatic lesion can be highly variable.

As a limitation of this study, there are conflicting data about the accuracy of CGM at low glucose levels. For instance, a euglycemic hyperinsulinemic clamp study showed that interstitial glucose concentrations could fall even when plasma glucose levels remained unchanged. Conversely, sen-
Figure 4. Continuous glucose monitoring before (A) and after (B) laparoscopic resection of the distal pancreatic tumor. A black arrow indicates a rapid decline in the blood glucose after excessive glucose infusion.

sor glucose levels might remain lower than plasma glucose levels during mild hypoglycemia and recovery from hypoglycemia (21). More accurate glucose sensors are needed for next-generation CGM in the near future.

In conclusion, it is important to consider insulinoma as a cause of postprandial hypoglycemia. CGM is useful not only for the detection of asymptomatic hypoglycemic events, including reactive hypoglycemia, but also for the evaluation of the treatment outcome.

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

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