Hypoglycemia Unawareness in Insulinoma Revealed with Flash Glucose Monitoring Systems

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Abstract:
The delayed diagnosis of insulinoma remains a clinical issue. One of the main causes of such a delay is hypoglycemia unawareness. A 53-year-old woman fell unconscious during postprandial exercises. Flash glucose monitoring (FGM) systems revealed glucose profiles with fasting hypoglycemia, which facilitated the clinical diagnosis of insulinoma even though she was unaware of her hypoglycemia. The preoperative comparison of the blood glucose values provided by FGM with those obtained from capillary blood were consistent. Thus, FGM may have potential utility in revealing the presence of insulinoma-induced hypoglycemia.

Key words: insulinoma, flash glucose monitoring, continuous glucose monitoring, hypoglycemia, DOTATOC, hypoglycemia unawareness

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Introduction

Insulinoma is a rare neuroendocrine tumor (1), accounting for 20.9% of all pancreatic endocrine tumors in epidemiological studies across Japan (2). Fasting hypoglycemia is known to be common in insulinoma and has diagnostic value, as more than 80% of patients with insulinoma demonstrate fasting hypoglycemia (3, 4). However, repeated and prolonged hypoglycemic episodes can reduce the awareness of neurogenic and neuroglycopenic hypoglycemic symptoms in insulinoma (5), which delays the diagnosis of insulinoma (6, 7).

Continuous glucose monitoring (CGM) has been successfully used to detect hypoglycemia in insulinoma cases with hypoglycemia unawareness (7, 8). However, currently available CGM systems in Japan require calibration by frequent self-monitoring of capillary blood glucose (CBG) levels, and patients without an insulin pump use can only view their CGM values retrospectively in consultation with their physicians (9). The flash glucose monitoring (FGM) systems Freestyle Libre Pro and Freestyle Libre (Abbot Diabetes Care, Oxon, UK) were recently approved for market in Japan. Due to their factory calibration, these two FGM systems require no CBG-based calibration, and the Freestyle Libre even allows patients ready access to check their current glucose levels and trends (10, 11). These features can facilitate the detection of unnoticed hypoglycemic events and the clinical diagnosis of insulinoma and will also improve patients’ health-related quality of life by allowing patients to avoid episodes of hypoglycemia while awaiting surgery.

We herein report a case of insulinoma presenting with hypoglycemic symptoms during postprandial exercise, in which FGM facilitated the detection of the patient’s unnoticed hypoglycemia.

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A 53-year-old woman was referred to our hospital for the evaluation and treatment of hypoglycemia. She experienced sudden unconsciousness during her postprandial walking in the afternoon. After her consciousness was spontaneously restored, she visited a nearby hospital and found that her serum insulin and C-peptide (7.2 μU/mL and 2.2 ng/mL, respectively) were relatively high despite a low plasma glucose level (42 mg/dL). Hyperinsulinemic hypoglycemia was suspected as the cause of her episodes of unconsciousness. She had no family history of hypoglycemia, diabetes or multiple endocrine neoplasia type 1, no remarkable dietary habits or excess alcohol consumption, and no medical or surgical history. On her admission to our hospital, the patient was alert and asymptomatic.

There were no remarkable findings on a physical examination. She reported no increased appetite and no marked body weight gain over the past 10 years. Fasting blood test revealed the existence of fasting hypoglycemia in addition to hypoglycemia during the daytime (Fig. 1a), which is generally unlikely in cases of reactive hypoglycemia. Based on the analysis of the mean absolute relative differences (MARDs) and absolute differences (AGlucose) in several different conditions, the FGM values were largely in accordance with the CBG values routinely measured using One-Touch² Ultra® (Johnson & Johnson Company, Vacaville, CA, USA) during her hospitalization (Table 2). She had no history of anti-diabetic agent use, and none of the laboratory data suggested other endocrine diseases (Table 1).

She was then subjected to a 72-h fasting test; however, the test was stopped approximately 7.5 hours after beginning because of her low point-of-care glucose level (44 mg/dL) for her safety, due to the possibility of hypoglycemia unawareness, although she remained asymptomatic (Fig. 1b and Table 3). Despite her low plasma glucose (46 mg/dL), her insulin (36.4 μU/mL) and C-peptide (5.43 ng/mL) values were high (Fajans index 0.79, Grunt index 1.26, Turner index 227.5). Despite her low plasma glucose (46 mg/dL), her insulin (36.4 μU/mL) and C-peptide (5.43 ng/mL) values were high (Fajans index 0.79, Grunt index 1.26, Turner index 227.5).

Abdominal dynamic computed tomography (CT) showed a tumor at the head of the pancreas that was 20 mm in diameter in the early and delayed phases (Fig. 2a and b). Despite no significant uptake on ¹⁸F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) (Fig. 2c), the tumor demonstrated a significant uptake on "Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N',N",N"-tetraacetic acid-D-Phe³-Tyr⁴-octreotide PET/CT (DOTATOC-PET/CT) (standardized uptake value [SUV]max = 22.9; Fig. 2d). Endoscopic ultrasonography (EUS) showed an isoechogenic homogenous tumor in the head of the pancreas. EUS-guided fine needle aspiration cytology revealed that the tumor was positive for insulin staining. Based on these findings, a clinical diagnosis of insulinoma was made.

The patient was discharged from our hospital to await her surgical operation. FGM using the Freestyle Libre system revealed hypoglycemia lasting almost 24 hours with evident hypoglycemia unawareness (Fig. 1c). Although the patient checked her glucose levels using the Freestyle Libre system...
Figure 1. Representative daily summaries of flash glucose monitoring (FGM). The findings of the FreeStyle Libre Pro (a) during the first hospitalization (upper panel: representative day, lower panel: summary of 10 days) and (b) on the day of the fasting test and (c) those of the FreeStyle Libre before the operation (upper panel: representative day, lower panel: summary of 14 days) and (d) 8 weeks after the surgical operation (upper panel: representative day, lower panel: summary of 14 days). The estimated calorie consumption was analyzed by a single-axial accelerometer Lifecorder (Suzuken Co., Tokyo, Japan), and the total daily energy intakes were calculated by our registered dieticians based on three-day food records. Black lines, blood glucose levels estimated by FGM; black dots, blood glucose levels estimated by self-monitoring of blood glucose using capillary blood; orange dots, self-checking of blood glucose levels estimated by FGM; black arrowheads, meals; white arrowheads, snacks; gray box, hypoglycemia periods without the patient’s awareness; black box, periods with exercise above medium strength.
over 15 times a day and consumed high-caloric foods and occasional snacks, prolonged hypoglycemia without the patient’s awareness was still observed throughout the day (Fig. 1c, Gray boxes). Despite our recommendations, she refused any preoperative drug therapy, including diazoxide. Thus, prompt surgery was planned in addition to dietary guidance.

Six weeks after admission after the initial admission, the patient underwent pancreatectoduodenectomy. A pathological examination revealed a tumor 23 mm in diameter at the head of pancreas (Fig. 3a and b). Immunohistochemical studies showed that the tumor was positive for chromogranin A (Fig. 3c) and synaptophysin as well as insulin (Fig. 3d) and somatostatin receptor (SSTR) type 2 (Fig. 3e) but negative for gastrin and glucagon. The Ki67 proliferative index of the tumor was 1.8%. The patient’s pathological staging was T2N0M0 (stage IB) and T2N0M0 (stage IIA) according to the AJCC/UICC and European neuroendocrine tumor society TNM staging system, respectively. Blood tests shown that the median time to a diagnosis is 24 months, with a range of up to 30 years (12). A delayed diagnosis of insulinoma can progressively induce coma or death (7, 8, 13) and remains a clinical issue (6, 14).

One of the main causes of a delay in the diagnosis of insulinoma is hypoglycemia unawareness. As previously shown, a lack of neurogenic and neuroglycopenic symptoms is not rare in patients with insulinoma (5). Repeated and prolonged hypoglycemia events cause hypoglycemia unawareness, which can obscure a patient’s notice and a physician’s suspicion of possible hypoglycemia. In fact, the present case developed sudden postprandial unconsciousness without any evident hypoglycemic episodes at fasting.

CGM systems have been used in insulinoma cases with hypoglycemia unawareness (7, 8). However, the requirement of frequent CBG-based calibrations and the inability of the patient to self-check CGM values remain major obstacles to the use of CGM systems as a modality for identifying hypoglycemia in insulinoma cases with hypoglycemia unawareness. FGM systems have been recently introduced as a tool to estimate blood glucose levels continuously based on inter-

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### Table 2. A Comparison between Flash Glucose Monitoring and Capillary Blood Glucose Values.

<table>
<thead>
<tr>
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<th>Number of time points analyzed</th>
<th>MARD (%)</th>
<th>ΔGlucose (mg/dL)</th>
</tr>
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<tbody>
<tr>
<td>Fasting</td>
<td>9</td>
<td>3.5±15.2</td>
<td>-2.7±8.3</td>
</tr>
<tr>
<td>Post-meal</td>
<td>28</td>
<td>11.6±16.1</td>
<td>-10.2±12.3</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>35</td>
<td>0.8±18.8</td>
<td>-0.4±10.0</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>8.1±17.7</td>
<td>-7.6±12.0</td>
</tr>
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The FGM values obtained by Freestyle Libre Pro 48 h after FGM sensor attachment were retrospectively compared with a total of 69 CBG values obtained by the OneTouch® Ultra®. The mean absolute relative difference (MARD) and ΔGlucose were calculated for not only all of the time points for which CBG values were available (Total) but also fasting (Fasting) and two hours after meals (Post-meal). MARD and ΔGlucose were also calculated for the time points at which the CBG values were within the hypoglycemic range (≤70 mg/dL). MARD is defined as 100×|FGM value - CBG value| / CBG value; ΔGlucose is defined as “FGM value - CBG value”.

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### Table 3. Laboratory Data of the Patient at the End of the Fasting Test.

<table>
<thead>
<tr>
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<th>At the End of the Fasting Test</th>
<th>20 min after i.v. 1mg glucagon</th>
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<tbody>
<tr>
<td>Plasma glucose (mg/dL)</td>
<td>46</td>
<td>95</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>36.4</td>
<td>123.8</td>
</tr>
<tr>
<td>C-peptide (ng/mL)</td>
<td>5.43</td>
<td>8.35</td>
</tr>
<tr>
<td>Acetoacetic acid (μmol/L)</td>
<td>30.1</td>
<td>-</td>
</tr>
<tr>
<td>3-β-hydroxybutyric acid (μmol/L)</td>
<td>14.7</td>
<td>-</td>
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</table>

A 72-h fasting test was performed after admission to our hospital for the investigation of spontaneous hypoglycemia. After confirming glucose levels<45 mg/dL using OneTouch® Ultra®, 1 mg glucagon was administered intravenously.

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**Discussion**

Insulinoma is a rare neuroendocrine tumor that produces excess endogenous insulin, resulting in hypoglycemia (6). The clinical diagnosis of insulinoma is established by both the presence of hypoglycemia with inappropriate insulin secretion and the identification of a tumor mass. Previous studies have shown that the median time to a diagnosis is 24 months, with a range of up to 30 years (12). A delayed diagnosis of insulinoma can progressively induce coma or death (7, 8, 13) and remains a clinical issue (6, 14).
Figure 2. Computed tomography (CT) and positron emission tomography (PET) images of the abdomen. (a) Early-phase and (b) delayed-phase contrast-enhanced CT revealed a tumor at the head of the pancreas. (c) \(^{68}\text{Ga}\)-labeled 1,4,7,10-tetraazacyclodecane-N,N',N'',N'''-tetraacetic acid-d-Phe\(^1\)-Tyr\(^2\)-octreotide PET/CT but not (d) \(^{18}\text{fluoro-deoxy-glucose PET/CT showed a significant uptake in the tumor.}

Figure 3. Histological and immunohistological findings of the tumor at the head of the pancreas. (a) A macroscopic image (arrow) and (b) Hematoxylin and Eosin staining of the tumor. The tumor was diffusely positive for chromogranin A (c), insulin (d), and somatstatin receptor type 2 (e).

Interstitial fluid glucose levels. FGM systems avoid frequent CBG-based calibrations by the users because of their factory calibration (10, 11, 15). In addition, the Freestyle Libre system, one such FGM device, can display the estimated blood
glucose values via a hand-held reader (10, 11, 15). The use of FGM in the present case not only facilitated the diagnosis of insulinoma, but also helped prevent severe hypoglycemia while the patient was awaiting her surgical operation (Fig. 1c).

However, there remains some debate concerning the accuracy of FGM systems in the hypoglycemic range (15, 16), although several studies have recently validated the FGM accuracy (9, 10). We did not directly compare the FGM values with plasma glucose levels, both the FGM (Freestyle Libre Pro) and CBG values were largely consistent (Table 2).

DOTATOC-PET/CT and FDG-PET/CT provided differing results in our case (Fig. 2c and d). The clinical usefulness of SSTR-targeted imaging, such as DOTATOC-, DOTATATE (DOTA-Nal3-octreotide)-, and DOTANOC (DOTA-Nal3-octreotide)-PET/CT, has been established for the diagnosis of neuroendocrine tumors (NETs) (17, 18). Furthermore, DOTATOC- and DOTATATE-PET/CT have shown a comparable diagnostic accuracy for NETs (19). However, the SSTR expression in insulinoma is reportedly less frequent than in other NETs (20). SSTR-targeted imaging has been reported to have for the diagnosis of insulinoma (21); a previous report described the superiority of SSTR-targeted PET/CT over conventional methods of localizing insulinoma (22). Despite only a few reports focusing on DOTATOC-PET/CT for the localization of insulinoma, the present case showed that DOTATOC-PET/CT is useful in some cases of insulinoma.

In summary, we herein described a case of insulinoma with hypoglycemia unawareness in which the diagnosis and treatment were facilitated by FGM use.

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

Acknowledgement
T.S., T.M., and D.Y. were involved in the clinical care and management of the patient and drafted the manuscript. R.K., M.T., S.O., E.J., K.W., A.Y., T.M., Y.N., Y.Y., Y.K., Y.I., M.O., and A.Y. were involved in the clinical care and management of the patient and contributed to the analysis and interpretation of the data. N.I. contributed to the analysis and interpretation of the data and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript. N.I. is the grantor of the manuscript.

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