Unmet needs in current clinical practice for insulinoma: Lessons from nationwide studies in Japan

Insulinoma is a rare pancreatic neuroendocrine neoplasm (PanNEN) that causes hypoglycemia owing to endogenous insulin hypersecretion. Insulinoma is the most common functional PanNEN; it is also one of the most common causes of hyperinsulinemic hypoglycemia in adults without diabetes mellitus1–4. However, little is known of recent clinical practice for insulinoma, especially the treatment strategy and unmet clinical needs, although some epidemiological studies have been reported1,3.

Insulinoma is usually benign and solitary, but some patients have malignant insulinoma and/or multiple tumors as part of the multiple endocrine neoplasia type 1 (MEN1) syndrome. Recently, Yamada et al.1 reported a nationwide questionnaire-based survey on endogenous hyperinsulinemic hypoglycemia in Japan in 2017–2018. The survey included 205 patients with insulinoma: 118 benign, 18 malignant, and 69 unknown. The median ages of onset for benign and malignant insulinoma were 53 (range: 5–88) and 49 (range: 24–86) years old, respectively. As for treatment, surgical resection was performed in 159 patients (77.6%), 118 of whom had benign insulinoma (100%) and 11 had malignant insulinoma (61.1%). However, it is noteworthy that the survey also included 69 patients classified as ‘unknown’ with regard to this factor, i.e., patients who had no information or answers on malignancy in their questionnaire; of them only 30 patients (43.5%) underwent pancreatectomy. Considering the very rare prevalence of malignant insulinoma, most of these patients with ‘unknown’-classified insulinoma were likely benign cases, suggesting that a non-negligible number of patients avoided surgery as a treatment option even though they were still relatively young (median: 58 years old).

Another nationwide study of insulinoma in Japan has been reported recently5. This study utilized the Diagnosis Procedure Combination (DPC) database, a nationwide inpatient database in Japan. The database covers almost 50% of acute-care inpatients in Japan and enables longitudinal observation from diagnosis to treatment including the postoperative period. The retrospective analysis using the dataset between 2010 and 2018 identified 946 patients with insulinoma: 844 with benign insulinoma and 102 with malignant insulinoma. The median ages of onset for benign and malignant insulinoma were 66 (range: 49–76) and 55.5 (range: 43–67) years old, respectively. As for treatment, surgical resection was performed in 667 patients (70.5%), 608 cases of benign insulinoma (72.0%) and 59 cases of malignant insulinoma (57.8%). Although 85% of the patients with benign insulinoma who were younger than 70 years were reported to have undergone surgery in this study, the low proportion of patients with benign insulinoma who underwent surgery was revealed in the longitudinal observation being a larger sample size compared with previous studies1,3. In addition to a common use of diazoxide, recently introduced medications including long-acting somatostatin analogs, such as octreotide and lanreotide, and everolimus, a mammalian target of the rapamycin inhibitor, may also contribute to avoiding surgery especially in malignant cases, while the long-term use of such agents especially in young cases with benign insulinoma should be carefully discussed in terms of adverse effects and cost effectiveness. Although such advances in medical treatment and the increasing age of the patient population should be considered, surgical resection remains the only curative treatment for insulinoma5. Taken together with these findings in the latest nationwide studies of clinical practice for insulinoma1,2, the achievement of cure in patients with insulinoma, even when benign, remains a clinical challenge.

What is a possible clinical obstacle to surgery and the cure of insulinoma? The patient characteristics including their relatively young age and the low proportion of MEN1-related cases in the benign insulinoma group in the DPC database study5 suggests that the main obstacle to curative treatment resides in the diagnostic procedure, especially preoperative tumor localization, rather than the surgical factors or techniques. The precise localization of an insulinoma is critical for curative surgery4,5, but remains challenging primarily due to the small tumor sizes4,5. Conventional imaging such as ultrasonography, computed tomography (CT), and magnetic resonance imaging have proven to display low sensitivity, selective arterial calcium stimulation test (SACST), and endoscopic ultrasound are invasive and operator-dependent6. While somatostatin receptor (SSTR)-targeted imaging approaches have improved the sensitivity, they are highlighted by a crucial limitation in that insulinomas may lack adequate expression levels of SSTR subtypes6. Thus, a novel non-invasive insulinoma-targeting imaging technique having higher resolution would facilitate surgical intervention and raise the cure rate of insulinoma (Figure 1).
Another unmet need in the clinical practice of insulinoma has been revealed by the recent nationwide studies\textsuperscript{1,2}. The DPC database study demonstrated that the prevalence of postoperative diabetes mellitus was 9.7\%; 9.4\% in benign cases and 13.6\% in malignant cases\textsuperscript{2}. Similarly, the questionnaire-based study showed the prevalence of postoperative diabetes mellitus was 15.8\% in all cases of pancreatic tumor, while that of residual hypoglycemia was 5.1\%\textsuperscript{1}. In addition, neurological impairment including dementia and epilepsy (10.7\%) was also observed. Both postoperative diabetes mellitus and residual hypoglycemia are partly related to the surgical resection strategy. More accurate preoperative tumor localization might thereby prevent residual hypoglycemia at the same time it may also avoid unnecessary segmental or subtotal resection of the pancreas and prevent the onset of postoperative diabetes mellitus. Moreover, considering that laparoscopic pancreatic surgery technique has become more feasible for insulinoma, more accurate preoperative localization might well contribute to a less-invasive surgical strategy. Therefore, novel clinical technology for more accurate tumor localization is desired.

Based on the exploration of target molecules specific to pancreatic \(\beta\) cells, such a novel strategy for non-invasive localization of insulinoma has emerged recently, i.e., glucagon-like peptide-1 receptor (GLP-1R)-targeted imaging techniques\textsuperscript{5,6}. Radiolabeled GLP-1R agonist exendin-4-based probes for single-photon emission computed tomography and positron emission tomography (PET) have been developed that are both less invasive and give more accurate localization of insulinoma in comparison with SACST and SSTR-targeted imagings\textsuperscript{5,7}. Additionally, an exendin-4 probe conjugated with polyethylene glycol (PEG) for PET, \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\), has been developed for the purpose of improving pharmacokinetics and probe delivery to the targeted tumors\textsuperscript{5}. A \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\) probe has proven to have acceptable clinical safety and to provide reasonable visualization of the human pancreas\textsuperscript{8}. Moreover, GLP-1R-targeted imaging techniques have been investigated also for the evaluation of pancreatic \(\beta\)-cell mass, which might contribute to determining the ideal resection area considering the personalized risk of diabetes\textsuperscript{6}. Thus, GLP-1R-targeted imaging should be promising for the accurate localization of insulinoma as well as providing a surgical strategy for maintaining glycemic control (Figure 1).

In summary, the recent nationwide studies on insulinoma revealed unmet needs in current clinical practice for insulinoma in Japan. The relatively low proportion of patients who actually underwent surgery, postoperative diabetes mellitus, and residual hypoglycemia have been found as clinical issues. These findings indicate that the achievement of cure in patients with insulinoma remains challenging and suggests an urgent need for exploring non-invasive insulinoma-targeting imaging. It may well provide more accurate localization and thereby encourage curative surgery as well as prevent postoperative diabetes mellitus or residual hypoglycemia. In this context, the recently developed GLP-1R-targeted imaging such as \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\) PET are promising and may fulfill these clinical unmet needs for insulinoma.

**DISCLOSURE**

D Y received clinical commissioned/joint research grants from Nippon Boehringer Ingelheim, Eli Lilly, Taisho-Toyama, MSD, Takeda, Ono, and Novo Nordisk Pharma. N I received clinical commissioned/joint research grants from Daiichi Sankyo, Terumo, and Drawbridge Inc.; speaker honoraria from Kowa, MSD, Astellas Pharma, Novo Nordisk Pharma, Ono Pharmaceutical, Nippon Boehringer Ingelheim, Takeda, Eli Lilly Japan, Sumitomo Dainippon Pharma and Mitsubishi Tanabe Pharma; scholarship grants from Kissei Pharmaceutical, Sanofi, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Takeda, Japan Tobacco, Kyowa Kirin, Sumitomo Dainippon Pharma, Astellas Pharma, MSD, Eli Lilly Japan, Ono Pharmaceutical, Sanwa Kagaku Kenkyusho, Nippon Boehringer Ingelheim, Nove

---

**Figure 1** | Unmet clinical needs for the management of insulinoma. Glucagon-like peptide-1 (GLP-1) receptor-targeted imaging such as that using \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\) positron emission tomography (PET) are promising and may fill unmet clinical needs. Structure of \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\) and a \([^{18}\text{F}]\text{FB(ePEG12)12-exendin-4}\) PET/computed tomography (CT) abdominal image of a healthy subject are shown.
Nordisk Pharma, Novartis Pharma, Teijin Pharma, and Life Scan Japan.

Takaaki Murakami1, Daisuke Yabe2, Nobuya Inagaki1*
1Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, Japan, 2Department of Diabetes and Endocrinology, Gifu University Graduate School of Medicine, Gifu, Japan

REFERENCES

1. Yamada Y, Kitayama K, Oyachi M, et al. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017–2018): congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata’s disease). J Diabetes Investig 2020; 11: 554–563.

2. Kurakawa KI, Okada A, Manaka K, et al. Clinical characteristics and incidences of benign and malignant insulinoma using a national inpatient database in Japan. J Clin Endocrinol Metab 2021; 106: 3477–3486.

3. Ito T, Igarashi H, Nakamura K, et al. Epidemiological trends of pancreatic and gastrointestinal neuroendocrine tumors in Japan: a nationwide survey analysis. J Gastroenterol 2015; 50: 58–64.

4. Murakami T, Yabe D, Inagaki N. Case 23-2018: a man with episodes of confusion and hypoglycemia. N Engl J Med 2018; 379: 1881–1882.

5. Murakami T, Fujimoto H, Hamamatsu K, et al. Distinctive detection of insulinoma using [18F]FB(ePEG12)12-exendin-4 PET/CT. Sci Rep 2021; 11: 15014.

6. Murakami T, Fujimoto H, Inagaki N. Non-invasive beta-cell imaging: visualization, quantification, and beyond. Front Endocrinol 2021; 12: 714348.

7. Wild D, Mäcke H, Christ E, et al. Glucagon-like peptide 1-receptor scans to localize occult insulinomas. N Engl J Med 2008; 359: 766–768.

8. Fujimoto H, Fujita N, Hamamatsu K, et al. First-in-human evaluation of positron emission tomography/computed tomography with [18F]FB(ePEG12)12-exendin-4: a phase 1 clinical study targeting GLP-1 receptor expression cells in pancreas. Front Endocrinol 2021; 12: 717101.

Doi: 10.1111/jdi.13730