

Molecular Imaging to the Surgeons Rescue: Gallium-68 DOTA-Exendin-4 Positron Emission Tomography-Computed Tomography in Pre-operative Localization of Insulinomas

Abstract

Background: Insulinoma is an islet-cell neoplasm that secretes insulin. It is usually localized to the pancreas and is often the most common cause of endogenous hyperinsulinemic hypoglycaemia in non-diabetic adult patients. Surgical excision with a curative intent is the standard modality of treatment, and it requires precise localization of tumor tissue. Ga-68 DOTA-exendin-4 PET/CT scan is a clinically reasonable and sensitive scan for the identification of insulinoma. The aim of this prospective cohort study was to determine the overall accuracy of Ga-68 DOTA-exendin-4 PET/CT scan in the detection of insulinoma. **Materials and Methods:** Eight patients with fasting hyperinsulinemic hypoglycaemia with neuroglycopenic symptoms were enrolled in this study which was conducted during October 2016 to October 2017. Whole body PET/CT scan was performed on a Philips time of flight PET/CT scanner, 60 minutes after injection of Ga-68 DOTA-exendin-4 (and also Ga-68 DOTANOC). The imaging findings were compared to the histopathological diagnosis in six out of eight patients and to subsequent follow up in the remaining two patients who did not undergo surgery. **Results:** The sensitivity of Ga-68 DOTA-Exendin-4 PET/CT scan in insulinoma detection was found to be 75%. **Conclusion:** Ga-68 DOTA-Exendin-4 PET/CT scan is highly sensitive for identification and exact localization of insulinoma which can guide better surgical exploration. However, randomised controlled trials are needed to assess the accuracy of Ga-68 DOTA-Exendin PET/CT scan in localization of insulinoma.

Keywords: Gallium-68 DOTA-exendin-4, Glucagon-like peptide-1, insulinoma, positron emission tomography-computed tomography scan

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Introduction

Insulinoma is an islet cell adenoma that secretes insulin. It is usually localized to the pancreas and is often the most common cause of endogenous hyperinsulinemic hypoglycemia in nondiabetic adult patients. Approximately 90% of insulinomas are single and benign but can be malignant in <10% of cases. About 5%–10% of the times, they can be multiple and are usually associated with multiple endocrine neoplasias Type 1. The incidence of insulinoma according to an observational study was about four cases per million with a median age of 50 years.^[1]

Patients with insulinoma often present with nonspecific symptoms such as palpitations, sweating, altered sensorium, confusion, weakness, and seizures. The diagnosis and management of insulinomas require a multidisciplinary approach, with careful

recognition of key clinical symptoms, relevant laboratory investigations, and imaging for accurate diagnosis. The diagnosis of insulinoma is confirmed by a supervised 72 h fasting test in a hospital setting in which inappropriately increased serum insulin levels are demonstrated despite the low blood glucose levels.^[2]

Noninvasive techniques such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are available for localization of insulinoma but have limitations due to low accuracy in diagnosing small-size tumors.^[2] Endoscopic ultrasonography has a sensitivity of 70%–95% in diagnosing insulinoma, but pancreatic tail lesions are often missed. Selective angiography and intra-arterial calcium stimulation with hepatic venous sampling for insulin levels can detect tumor in 60% and 80% of cases, respectively.^[3,4] Somatostatin

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receptor scintigraphy (SRS), which is considered to be the most sensitive investigation to detect well-differentiated neuroendocrine tumors, performs poorly in detecting insulinomas. This is due to the low expression of subtype-2 somatostatin receptors.^[5]

Glucagon-like peptide-1 (GLP-1) receptors are present in the pancreas, blood vessels, stomach, or parafollicular C cells. Reubi *et al.* have demonstrated in their study that these receptors are overexpressed in benign insulinoma which is a target for molecular imaging.^[5] In recent years, GLP-1 receptor (GLP-1R) targeted imaging has been established in the detection of insulinoma, as GLP-1 receptors are overexpressed in these tumors.^[6]

Exendin-4 is a 39-amino acid peptide, extracted from saliva of the Gila monster, similar to mammalian incretin GLP-1 which binds and activates the GLP-1R on pancreatic β -cells.^[7] Clinical studies with In-111- and Tc-99 m-labeled exendin-4 imaging showed high sensitivity in identifying insulinomas with single-photon emission CT (SPECT).^[8,9] However, Gallium-68 (Ga-68) DOTA-exendin-4 positron emission tomography-CT (PET/CT) scan has a benefit of higher sensitivity, image contrast, and spatial resolution over SPECT.^[10]

Most recently, a pilot study showed that Ga-68 DOTA-exendin-4 PET/CT scan is a clinically reasonable and sensitive scan for the identification of insulinoma.^[11]

In this study, we are describing our experience with Ga-68 DOTA-exendin-4 PET/CT scan in the detection of insulinoma.

Materials and Methods

Patients

In this prospective cohort study, conducted between October 2016 and October 2017, eight patients with fasting hyperinsulinemic hypoglycemia with neuroglycopenic symptoms were enrolled with the following inclusion criteria: biochemically proven endogenous hyperinsulinemic hypoglycemia (plasma glucose concentration <3.0 mm, insulin >3 μ U/mL, and C-peptide >0.6 ng/mL) and a negative screening for sulfonyleurea. The patients ranged between 6 months to 60 years with a median age of 32 years with a male-to-female ratio of m:f = 5:3. In addition to the conventional preoperative localization methods for insulinoma, patients were referred for Ga-68 DOTA-exendin-4 PET/CT before elective surgery. All imaging procedures were performed within 1 month of diagnosis. The presence of tumor was subsequently confirmed histopathologically, and the histologic type was determined. The study was approved by the Institutional Review Board of Fortis Memorial Research Institute, Gurgaon. Written informed consent was obtained from each patient before the procedure.

Preparation of Gallium-68 DOTA-exendin-4

Synthesis and labeling of Ga-68 DOTA-exendin-4 were done as described. Ga-68 was eluted from Ge-68/Ga-68 generator systems (1850 MBq; Isotope Technologies Garching, GmbH, Germany) in 0.1 M hydrochloric acid. The first fraction of 1.5 ml from the generator was discarded and the next 1.5 ml, containing over 90% of the total radioactivity, was collected and buffered with 1.5 ml of acetate buffer to provide a pH of 4.5 ± 0.4 . Then, 25 nmol of exendin-4 (ABX, Radeberg, Germany) was added and the reaction mixture was incubated at 90°C for 30 min. The labeled product was purified using preconditioned TC-18 (Sep-Pak Plus Short Cartridge, Waters) solid-phase extraction cartridge, eluted in 2 ml ethanol, and passed through a 0.22 μ m filter. A sample was taken for the determination of identity, pH, and radiochemical purity. The product with radiochemical purity of at least 95% was used for patient studies.

Gallium-68 DOTA-exendin-4 positron emission tomography-computed tomography

Patient fasted for at least 4 h before imaging. A continuous infusion of 5% dextrose saline was administered to prevent hypoglycemic episode during the period of fasting. 74–111 mbq (2–3 mCi) of Ga-68 DOTA-exendin-4 was administered intravenously. Whole-body PET/CT scan was performed on a Philips time of flight PET/CT scanner (TruFlight), 60 min after injection of radiopharmaceutical with a 2–3 min per bed position. Images were reconstructed using iterative ordered subset expectation maximization-based reconstruction. Scans were read by two independent qualified nuclear medicine physicians using dedicated Philips workstations.

Results

Eight patients were recruited in the study. The demographic, clinical characteristics, and biochemical investigations are summarized in Table 1.

Imaging could demonstrate focal/segmental Ga-68 DOTA-exendin-4 uptake with mean maximal standardized uptake value (SUV_{max}) of 21 ± 5 (SUV_{max}: 25) [Figure 1a and b] in three of eight patients as shown in Table 2. The corresponding CT images demonstrated arterial enhancing lesions. Other five patients did not show any Ga-68 DOTA-exendin-4 uptake higher than background.

Six patients underwent laparotomy. Three patients with positive scan results were proven as insulinoma on histopathological examination [Figure 2a and b]. These patients were free of hypoglycemia symptoms in the postoperative period.

The other three patients with negative scan results were explored due to the persistence of hypoglycemic symptoms. Nesidioblastosis (patient 4), noninsulinoma pancreatogenous hypoglycemia syndrome (patient 6), and insulinoma (patient 7) were diagnosed based on the histopathological examination

Table 1: Clinical characteristics

Characteristic	Age (years)	Sex	Presenting symptoms	Secretes insulin (range: 4-23 μ U/mL)	C-peptide (range: 0.3-3.7 ng/mL)	Surgical procedure	Histopathology
Patient 1	38	Male	Hypoglycemia, seizures, and dizziness	140	8.4	Pancreatic head resection	Insulinoma
Patient 2	43	Male	Recurrent loss of consciousness and hypoglycemia	1000	23.06	Whipple's surgery	Insulinoma
Patient 3	5	Female	Hypoglycemia and dizziness	36	4.3	Pancreatic body and tail resection	Insulinoma
Patient 4	6 months	Female	Hypoglycemia	44	7	Pancreatic head resection	Nesidioblastosis
Patient 5	57	Male	Hypoglycemia	4.1	0.92	-	-
Patient 6	42	Male	Hypoglycemia and seizures	25	5.25	Pancreatic head resection	NIPHS
Patient 7	7	Male	Hypoglycemia	40	NA	Enucleation (at the tail of pancreas)	Insulinoma
Patient 8	27	Female	Hypoglycemia and dizziness	20	3.5	-	-

NA: Not available, NIPHS: Noninsulinoma pancreatogenous hypoglycemia syndrome

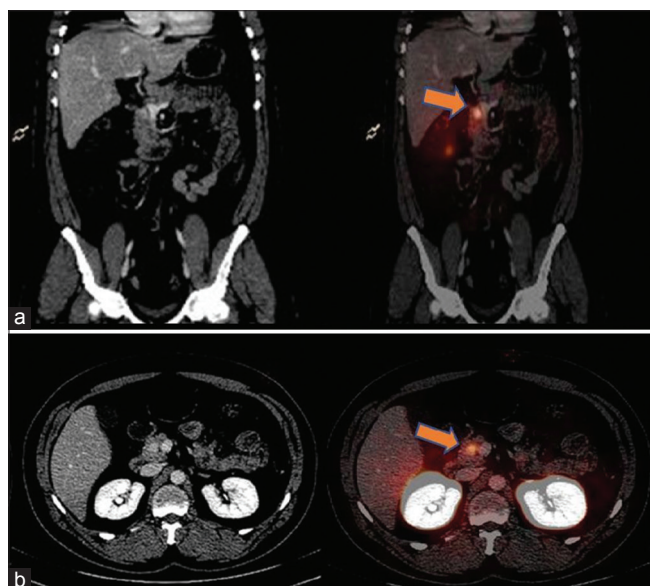


Figure 1: (a) The coronal and (b) transaxial images of contrast computed tomography abdomen (left) and Gallium-68 DOTA-exendin-4 positron emission tomography-computed tomography scan images (right) of patient 1 obtained 90 min after the injection of 74 MBq of Gallium-68-DOTA-exendin-4 demonstrating focal (arrow) uptake in the head of pancreas

of operated specimen [Table 1]. None of these patients were positive for malignant insulinoma.

The other two patients with negative scan results were not subjected to surgical management. They were subsequently found to have antibodies to insulin (patient 5) and prediabetic state (patient 8).

The sensitivity of Ga-68 DOTA-exendin-4 PET/CT scan in insulinoma detection was found to be 75%.

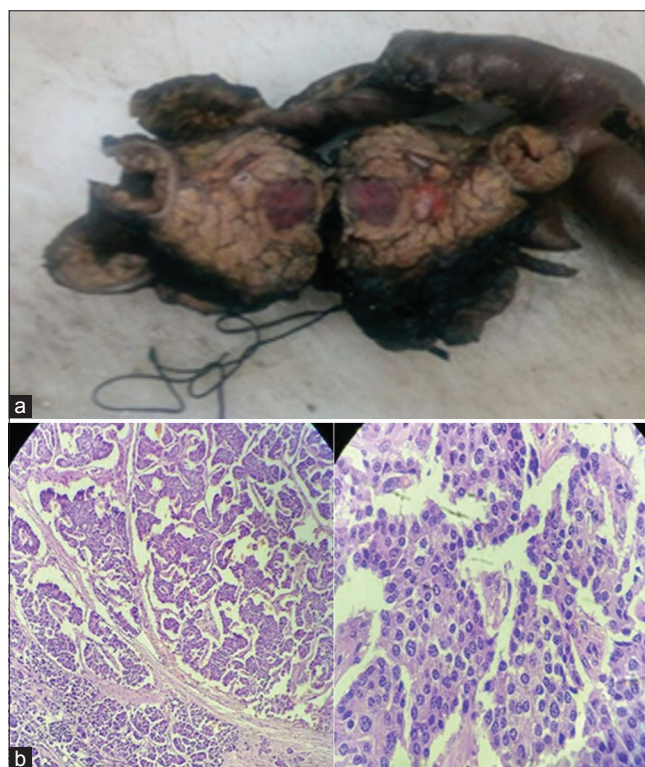


Figure 2: (a) The image showing surgically removed gross specimen. (b) The image of hematoxylin and eosin-stained slide showing insulinoma

Discussion

Insulinoma is a neuroendocrine tumor of the beta-cells of the pancreas. It is characterized by the triad of hypoglycemia, symptoms related to hypoglycemia, and resolution of symptoms by glucose administration.^[2]

Table 2: Preoperative imaging compared to histopathology as gold standard

Conventional imaging	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
CT scan	FN	TP	FN	TN	TN	TN	NA	TN
MRI	TP	TP	TP	TN	NA	TN	NA	NA
⁶⁸ Gallium-DOTA-exendin-4 PET/CT								
Detection of tumor	TP	TP	TP	TN	TN	TN	FN	TN
SUVmax of background (Uncinate process of pancreas)	4	3	6					
SUVmax of tumor	18	20	25					

SUVmax value: Maximal standardized uptake value, NA: Not available, TP: True positive, TN: Negative, FN: False negative, MRI: Magnetic resonance imaging, CT: Computed tomography, PET: Positron emission tomography, Ga-68: Gallium-68

Due to low accuracy in the diagnosis of insulinoma with noninvasive imaging, Guettier *et al.*^[3] and McLean^[4] suggested that intra-arterial calcium stimulation and endoscopic ultrasonography can identify tumors with sensitivity of 70% and 80%, respectively. However, these investigations are invasive and costly and require expertise of an experienced interventional radiologist.

Ehehalt *et al.* suggested that nuclear medicine imaging, such as SRS, shows sensitivity of 50%–60% in diagnosing benign insulinomas.^[12] Somatostatin receptor imaging has high accuracy in identifying primary, recurrent, and metastatic gastrointestinal and pancreatic well-differentiated neuroendocrine tumors in comparison to CT scan and MRI. However, sensitivity for the identification of insulinoma is poor as insulinoma expresses low somatostatin receptor.^[5]

GLP-1Rs are overexpressed in benign insulinoma which is a target for molecular imaging.^[5] Wild *et al.* performed the first study in two patients with insulinoma with a labeled GLP-1R analog ([Lys40(Ahx-DTPA–111In)NH₂]-exendin-4).^[9] Subsequently, Christ *et al.*^[10] showed that imaging with In-111- and TC-99 m-labeled exendin-4 has high sensitivity in identifying insulinoma with SPECT. However, poor spatial resolution and anatomical description led to the development of GLP-1R targeting PET/CT tracers.

There are several studies which show that GLP-1R imaging is sensitive in identifying and localizing insulinomas. As GLP-1R receptors are overexpressed in these tumors, Ga-68 DOTA labeled with GLP-1R analog exendin-4 and PET/CT scan shows promising results in identification and exact localization of the tumor.^[7] Antwi *et al.* in their pilot study found higher spatial resolution, possibility of quantification, and lower radiation in Ga-68-DOTA-exendin-4 PET/CT scan.^[11]

In concordance with other recent studies^[3,10,13,14] in our study, eight patients who had biochemically proven fasting hyperinsulinemic hypoglycemia underwent Ga-68 DOTA-exendin-4 PET/CT scan, of which three patients showed focal uptake of Ga-68 DOTA-exendin-4 in pancreas which was suggestive of the possibility of insulinoma.

These three patients with positive scan results underwent surgery and were histologically proved as insulinoma and even hypoglycemic symptoms were reduced after surgery. In these three cases, Ga-68 DOTA-exendin-4 PET/CT scan was crucial in planning for surgery and had significant influence on the clinical management decisions by accurate identification and localization of the small lesion.

The other five patients who showed negative scan results were subjected for delayed scan after 2 h which did not show any focal Ga-68 DOTA-exendin-4 uptake.

One patient with negative scan results was explored because of the persistence of hypoglycemia symptoms (patient 7). The lesion was found to be localized at the tail of pancreas using intraoperative ultrasonography and proved as insulinoma based on histopathological examination. The lesion was 0.5 cm and located at the tail of pancreas which is often difficult to localize on PET-CT due to the limitation of spatial resolution. The patient was symptom free postoperatively.

Two patients with histologically proven nesidioblastosis (patient 4) and noninsulinoma pancreatogenous hypoglycemia syndrome (patient 6) showed negative results in Ga-68 DOTA-exendin-4 PET/CT scan. The reason for the negative scan in nesidioblastosis could be due to less number of GLP-1R in the nesidioblastosis than in benign insulinomas. There is one case report which showed positive results in nesidioblastosis with Ga-68 DOTA-exendin-4 PET/CT scan.^[14] Patient 4 also underwent F-18 DOPA PET-CT scan initially and the result was negative. These two patients were found to be free of hypoglycemia symptoms in the postoperative period.

The other two patients with negative scan results were not subjected to surgical management. Patient 5 was found to have serum insulin antibodies and patient 8 was diagnosed as prediabetic state.

The high incidence and density of GLP-1R expression in insulinoma were confirmed by pathological studies.^[6] In our study, Ga-68 DOTA-exendin-4 PET/CT scan exhibits high SUVs in all positive scans with mean SUVmax of 21 ± 5 which were compared with SUVmax of uncinat

process of the pancreas (background SUVmax). The sensitivity of Ga-68 DOTA-exendin-4 PET/CT scan in localizing insulinoma is 75% which is concordant with the results reported by Luo *et al.*^[15] The advantage of Ga-68 DOTA-exendin-4 PET/CT scan is good spatial resolution which helps in tumor quantification, identification, and exact localization of tumor preoperatively. Hence, they can be used to guide surgical management, thereby improving the success rate of surgical excision.

For academic interest, we also did Ga-68 DOTANOC PET/CT scan in all these eight patients. The results were negative in seven patients, but one patient (patient 4) showed focal area of Ga-68 DOTANOC uptake in pancreatic head which was found to be nesidioblastosis on postoperative histopathology. The reason for Ga-68 DOTANOC uptake could not be determined in this case.

The limitations of the study include small sample size and nonrandomization of data.

Conclusion

Ga-68 DOTA-exendin-4 PET/CT scan is highly sensitive for identification and exact localization of insulinoma which can guide better surgical exploration. However, randomized controlled trials are needed to assess the accuracy of Ga-68 DOTA-exendin-4 PET/CT scan in the localization of insulinoma.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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