Postprint: Technical Specifications for GLP-1 Receptor PET/CT Localization of Insulinoma

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Abstract

The diagnosis and surgical treatment of insulinoma rely on accurate localization through imaging examinations. GLP-1 (glucagon-like peptide-1) receptor imaging targeting pancreatic -cells has emerged as a highlight in insulinoma imaging research in recent years, and the clinical promotion of 68Ga-exendin-4 for GLP-1 receptor PET/CT imaging is recommended for localization diagnosis of insulinoma. For rare malignant insulinomas, GLP-1 receptor PET/CT combined with somatostatin receptor imaging can be employed for molecular imaging evaluation. 18F-DOPA PET/CT may be selected as a second-line nuclear medicine imaging localization method for insulinoma.

Full Text

Procedure Guideline of Glucagon-Like Peptide-1 Receptor PET/CT in Localizing Insulinoma

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Abstract

The diagnosis and surgical treatment of insulinoma depends on accurate localization through imaging modalities. Glucagon-like peptide-1 (GLP-1) receptor

imaging, which targets pancreatic -cells, has emerged as a highlight in insulinoma imaging research in recent years. Clinical use of Ga-exendin-4 for GLP-1 receptor PET/CT imaging is recommended for localizing insulinoma. For rare malignant insulinomas, combined GLP-1 receptor and somatostatin receptor imaging is recommended for molecular imaging evaluation. [1] F-DOPA PET/CT may be selected as a second-line nuclear medicine imaging method for localizing insulinoma.

Keywords: glucagon-like peptide-1 receptor, Ga-exendin-4, insulinoma

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Insulinoma is the most common functional pancreatic neuroendocrine tumor, accounting for 1–2% of pancreatic neoplasms with an incidence of approximately 0.4 per 100,000 per year (1). It is also the most common cause of organic hyperinsulinemic hypoglycemia in adults, clinically manifesting as recurrent episodes of hyperinsulinemic hypoglycemia accompanied by symptoms and signs of sympathetic nervous system activation and central nervous system suppression. Approximately 90% of insulinomas are benign and solitary, while 10% are malignant (defined by the presence of metastases), which may involve lymph nodes, liver, peritoneum, and other sites. Additionally, 5–10% of insulinomas are associated with hereditary diseases such as multiple endocrine neoplasia type 1.

The diagnosis of insulinoma first relies on establishing clinical symptoms and endogenous hyperinsulinemia. Imaging localization serves not only as an important basis for distinguishing insulinoma from other diseases causing endogenous hyperinsulinemic hypoglycemia but also as a critical guide for surgical intervention. Commonly used imaging methods for insulinoma localization include contrast-enhanced CT, MRI, endoscopic ultrasound, angiography, and selective arterial calcium stimulation with hepatic venous sampling for insulin measurement. However, each of these methods has limitations. Literature reports indicate that contrast-enhanced CT and MRI have variable diagnostic sensitivities of 60–85% for insulinoma, with lower sensitivity for moderately enhancing tumors or those adjacent to blood vessels (2, 3). Endoscopic ultrasound achieves 80–90% sensitivity for insulinomas in the pancreatic head and neck but is less effective for lesions in the body and tail of the pancreas or for ectopic insulinomas, and its accuracy is operator-dependent (3–5). Angiography and selective arterial calcium stimulation are invasive procedures with numerous factors affecting accuracy, and angiography only demonstrates high sensitivity for hypervascular insulinomas, with decreased sensitivity for moderately vascular lesions. Historically, intraoperative pancreatic exploration with intraoperative ultrasound has been considered the "gold standard" for localization, yet this method' s sensitivity is only approximately 80% (1). Therefore, identifying more sensitive and accurate imaging localization methods remains an important clinical challenge in the management of insulinoma.

Nuclear medicine imaging technology reflects pathophysiological processes and molecular biological information, offering unique "functional imaging" advantages that conventional imaging cannot match. Since insulinomas originate from pancreatic -cells, GLP-1 receptor imaging that targets these -cells has emerged as a highlight in recent insulinoma imaging research. This article will focus on GLP-1 receptor imaging, introducing its application overview and technical specifications in insulinoma. Somatostatin receptor imaging and ^{1} F-DOPA PET/CT also have certain applications in insulinoma diagnosis, and their applicable scopes and general research status will be discussed.

Overview of GLP-1 Receptor Imaging

Imaging Target: The GLP-1 Receptor Under physiological conditions, GLP-1 receptors are specifically expressed in only a few human tissues including the pancreas, duodenum, and neurohypophysis, with relatively high expression levels in pancreatic islet cells (6). While some early studies suggested GLP-1 receptor expression in - and -cells in addition to -cells (7, 8), subsequent research has refuted this, demonstrating that GLP-1 receptor mRNA and protein are present exclusively in pancreatic -cells (9). In insulinomas, GLP-1 receptor expression is extremely high, approximately 6–12 times that of normal -cells, representing the highest receptor expression level discovered in insulinomas to date. Moreover, over 90% of insulinomas share this molecular characteristic of GLP-1 receptor expression (6, 10). GLP-1 receptors are only expressed at low levels and with low frequency in a few other neuroendocrine tumors such as gastrinomas, VIPomas, pheochromocytomas, and bronchial carcinoids, and are not expressed in epithelial tumors or lymphomas (6, 10). This expression pattern enables GLP-1 receptor-targeted molecular imaging to achieve both excellent sensitivity and specificity for insulinoma, conferring substantial clinical research and application value.

Tracer Core Compound: Exendin-4 The natural ligand of GLP-1 receptors is GLP-1, a 36-amino-acid peptide secreted by intestinal L-cells that peaks postprandially. Binding to -cell GLP-1 receptors activates intracellular second messengers, promoting insulin release, inhibiting gastric emptying and glycogenolysis, and stimulating -cell proliferation while suppressing apoptosis (11). However, GLP-1 is rapidly cleaved by dipeptidyl peptidase IV (DPP-IV) in vivo, with a half-life of only 2 minutes (12), making it unsuitable for tracer preparation.

Exendin-4, isolated from Gila monster saliva, is a GLP-1 analogue containing 39 amino acids with 53% homology to GLP-1 and acts as a GLP-1 receptor agonist. Exendin-4 exhibits similar receptor affinity to GLP-1 (14), undergoes cellular internalization with low washout rates (15, 16), and most importantly, is resistant to DPP-IV cleavage, with over 70% remaining intact after 24 hours in vivo (17, 18). Consequently, GLP-1 receptor imaging tracers are primarily based on various radiolabeled exendin-4 compounds.

Clinical Research on GLP-1 Receptor Imaging Since 2002, exendin-4 has been labeled with multiple radionuclides (including ^{12}I, ^{123}I, ^{111}In, Tc, Ga, ^{1}F, Cu) for in vitro and animal model studies, validating the specificity and stability of these radiolabeled exendin-4 tracers for GLP-1 receptor binding. Biodistribution experiments and small-animal imaging in insulinoma models confirmed extremely high tracer uptake in insulinomas with excellent target-to-background ratios (15, 19–24), laying the foundation for clinical translation.

In 2008, the *New England Journal of Medicine* reported two cases of occult insulinoma, marking the first clinical application of GLP-1 receptor imaging (25). Both cases showed no abnormalities on conventional imaging, while ^{111}In-labeled exendin-4 ([Lys (Ahx-DTPA-^{111}In)NH]exendin-4) nuclear medicine imaging successfully localized the insulinoma lesions. Prior to 2014, GLP-1 receptor imaging primarily utilized ^{111}In- or Tc-labeled exendin-4 for single-photon emission computed tomography (SPECT). Three small clinical studies (totaling 47 cases of endogenous hyperinsulinemic hypoglycemia with clinical suspicion of insulinoma) demonstrated sensitivities of 95–100% for insulinoma localization, with positive predictive values of 83% (26–28).

Building upon GLP-1 receptor SPECT/CT research, positron emission tomography (PET) with superior spatial resolution and image signal-to-noise ratio became the next research direction, which is particularly important for insulinoma imaging since most lesions are <2 cm. High-resolution PET/CT imaging offers potential for further improving diagnostic sensitivity for small insulinomas (29). Since 2014, Peking Union Medical College Hospital has conducted prospective clinical research on GLP-1 receptor PET/CT imaging (using Ga-labeled exendin-4), maintaining the largest insulinoma study cohort and reporting the largest case series on GLP-1 receptor PET/CT for insulinoma diagnosis (30–34), placing our center at the international forefront in this field. In our cohort of over 210 patients with clinically suspected insulinoma, Ga-exendin-4 GLP-1 receptor PET/CT demonstrated a diagnostic sensitivity of 99.1%, significantly higher than pancreatic perfusion CT (80.7%), pancreatic MRI (78.9%), endoscopic ultrasound (79.2%), and somatostatin receptor imaging (22.8%). Furthermore, GLP-1 receptor PET/CT achieved 100% diagnostic specificity, superior to pancreatic perfusion CT (83.7%), pancreatic MRI (77.3%), and endoscopic ultrasound (80.0%). Given these excellent diagnostic performance characteristics, GLP-1 receptor PET/CT warrants clinical implementation and promotion to improve insulinoma management.

Technical Operation Specifications for Insulinoma GLP-1 Receptor PET/CT

Purpose and Indications GLP-1 receptor imaging is indicated for patients with clinically confirmed endogenous hyperinsulinemic hypoglycemia and suspected insulinoma to differentiate the cause of hyperinsulinemia and localize insulinoma lesions.

Pre-Examination Preparation **1. Patient Diet:** Since food intake stimulates endogenous GLP-1 secretion from the small intestine, which may compete with the tracer for GLP-1 receptor binding, patients should fast for approximately 2 hours before the examination to minimize endogenous GLP-1 secretion. During fasting, intravenous fluids may be administered to maintain blood glucose levels above 5 mmol/L.

2. Renal Protection: Exendin-4 tracers are excreted via the kidneys, undergoing glomerular filtration and proximal tubular reabsorption, with radiolabeled fragments retained in tubular cells (35). To minimize renal radiation dose and reduce intense renal uptake that may obscure pancreatic visualization (particularly the pancreatic tail), intravenous infusion of 200–500 ml succinylated gelatin injection (Gelofusine) should be initiated 0.5–1 hour before examination to inhibit tubular reabsorption of exendin-4 tracers.

3. History Taking: Relevant hypoglycemia history should be obtained, including onset time, frequency, venous blood glucose and simultaneous insulin/C-peptide levels during hypoglycemic episodes, prior pancreatic contrast-enhanced or perfusion CT, MRI, endoscopic ultrasound, and surgical history to guide PET/CT scanning protocols and image interpretation.

Tracer Preparation and Quality Control Due to the complex labeling process and low reaction yield of ^{1} F-labeled peptides, the long half-life (T / = 12.7 h) and high radiation dose of Cu, and the simple, efficient labeling process with moderate half-life (T / = 68 min) of Ga, Ga-labeled exendin-4 is recommended for GLP-1 receptor PET/CT imaging. The Ga generator availability and low cost further facilitate clinical implementation.

Ga-exendin-4 Preparation: Elute the Ge/ Ga generator with 0.1 mol/L hydrochloric acid (elution concentration per specific generator model instructions). Add 1 ml of GaCl eluate to 85–90 L of 1.25 mol/L sodium acetate to adjust pH to 3.5–4.0. Add 25–50 g of NOTA-MAL-cys -exendin-4 precursor to the mixture and heat at 100 °C for 10 minutes. Dilute the mixture to 5 ml with water for injection and pass through a Sep-Pak C18 Plus Light solid-phase extraction column. Elute the C18 column with 0.5 ml of 75% ethanol and collect the eluate to obtain the product. Dilute the product with water for injection (to achieve ethanol concentration <10%) and filter through a 0.22- m sterile filter to obtain Ga-exendin-4 injection (32).

Ga-exendin-4 Quality Control and Precautions: The Ga-exendin-4 product must undergo quality control via high-performance liquid chromatography or thin-layer chromatography, with radiochemical purity >98%. Since exendin-4 has glucose-lowering effects, precursor quantity should be minimized according to actual labeling yield and specific activity to control the final injected exendin-4 chemical amount (recommended not to exceed 20 g).

GLP-1 Receptor PET/CT Examination Method 1. Ga-exendin-4 Tracer Injection: Measure venous or fingertip blood glucose before tracer injection to assess hypoglycemia risk during examination. Inject Ga-exendin-4 tracer intravenously by slow push; the recommended dose is 37–74 MBq (minimum 18 MBq). Blood glucose reaches its nadir approximately 40 minutes after exendin-4 injection, with an average decrease of 1.3 mmol/L (range 0–2.6 mmol/L) (26, 27). Monitor patient condition during this period; if hypoglycemia or hypoglycemic symptoms occur, administer 50% glucose solution intravenously or orally until symptoms resolve. If pre-injection blood glucose is <4 mmol/L, initiate intravenous infusion of 5% or 10% glucose solution immediately after tracer injection. Approximately 5% of patients may experience tachycardia, mild nausea, or vomiting after Ga-exendin-4 injection (26, 32), typically occurring within 30 minutes and requiring no special intervention. No long-term adverse reactions have been reported.

2. PET/CT Scanning: PET/CT images can be acquired from 30 minutes to 3 hours post-injection, with acquisition recommended at 30–90 minutes. Determine the scan field based on clinical presentation; single-bed acquisition covering pancreas + liver may be selected, with the pancreas positioned centrally in the field to avoid edge artifacts. If distant metastasis is suspected, extend the scan range to neck-chest-abdomen-pelvis. Adjust PET acquisition time according to scan field, injected dose, and PET device performance. For low-dose injections (<37 MBq), single-bed scanning is recommended at 6–10 minutes/bed; for multi-bed scanning, adjust acquisition time based on PET instrument performance, number of beds, injected dose, and patient tolerance. Since the pancreatic tail is close to the left kidney, renal uptake may occasionally interfere with pancreatic tail lesion visualization (10, 26, 32). If no definite positive lesions are identified on initial scanning, delayed single-bed pancreatic scanning may be performed 2–3 hours post-injection (30, 32) (exendin-4 tracer has a longer effective half-life in insulinomas than in kidneys), with acquisition time of 10–15 minutes/bed.

3. Radiation Dose: The whole-body absorbed dose equivalent of Ga-exendin-4 is 0.016 mSv/MBq, with kidneys being the organ receiving the highest dose at 0.276 mSv/MBq (36).

Normal and Abnormal Image Interpretation 1. Normal Images: Due to urinary excretion, normal physiological uptake is observed in both kidneys and bladder. Mild homogeneous uptake is seen in the pancreas, with mild homogeneous uptake also possible in liver and spleen (Figure 1 [Figure 1: see original paper]). Since GLP-1 receptors have some physiological expression in duodenal Brunner' s glands (6), focal increased uptake may appear in the duodenum (26, 27, 30). Therefore, precise anatomical localization via co-registered CT is crucial to avoid confusion between physiological duodenal uptake and pancreatic head lesions (Figure 2 [Figure 2: see original paper]).

Figure 1. Normal Ga-exendin-4 PET maximum intensity projection image showing uniform physiological uptake in the pancreas.

Figure 2. Ga-exendin-4 PET/CT in an insulinoma patient: (A) Ga-exendin-4 PET maximum intensity projection image; (B, C) transaxial fusion images. Abnormally increased Ga-exendin-4 uptake is seen in an insulinoma at the pancreatic uncinate process (long arrows in A, B), with a focally mildly increased uptake area in the duodenum (short arrowheads in A, C), and diffuse uniform physiological uptake in the pancreatic neck, body, and tail (long dashed arrows in A, C).

2. Abnormal Images: Any focal area of increased radioactivity in or outside the pancreas is considered abnormal and diagnosed as an insulinoma lesion (Figure 3 [Figure 3: see original paper]).

Figure 3. (A–B) Ga-exendin-4 PET/CT in a patient with pancreatic uncinate process insulinoma (A. PET maximum intensity projection image; B. transaxial fusion image) showing abnormally increased tracer uptake in the uncinate process insulinoma (long arrows in A, B) and mild physiological uptake in the pancreatic neck, body, and tail (short arrowheads in A). (C–D) Ga-exendin-4 PET/CT in a patient with insulinoma liver metastases (C. PET maximum intensity projection image; D. transaxial fusion image) showing numerous liver metastases with abnormally increased uptake (short arrows in D) and markedly increased uptake in the primary insulinoma lesion in the pancreatic body and tail (long arrow in D).

Value of Other Nuclear Medicine Imaging Techniques in Insulinoma Diagnosis

Somatostatin Receptor Imaging Somatostatin receptor imaging is the most accurate imaging method for diagnosing gastroenteropancreatic neuroendocrine tumors. However, since most insulinomas do not express or only weakly express somatostatin receptor subtype 2 (10, 37), its sensitivity for diagnosing insulinoma is only approximately 20–60% (32, 38–42). Therefore, somatostatin receptor imaging is not recommended as a first-line imaging modality for insulinoma.

While 90% of insulinomas are benign, approximately 10% are malignant. Benign insulinomas almost universally express GLP-1 receptors. In contrast, malignant insulinomas express GLP-1 receptors in only about 36% of cases (10, 43), suggesting that GLP-1 receptor imaging may have limited detection efficiency for malignant insulinoma lesions. Notably, malignant insulinomas that do not express GLP-1 receptors consistently express somatostatin receptor subtype 2, indicating that malignant insulinomas possess two distinct molecular expression patterns: either GLP-1 receptor or somatostatin receptor expression (43). Preliminary clinical studies have also shown that malignant insulinomas negative on GLP-1 receptor imaging are positive on somatostatin receptor imaging (28, 43). Therefore, in the imaging evaluation of insulinoma, somatostatin receptor imaging should be considered a second-line method when clinical suspicion for malignant insulinoma exists, such as: (1) suspicious metastatic lesions on

CT/MRI, (2) patients with multiple endocrine neoplasia type 1, or (3) cases with high clinical suspicion of insulinoma but negative GLP-1 receptor imaging.

Common somatostatin receptor imaging tracers include Tc-, ^{111}In-, and Ga-labeled somatostatin analogues (SSA) such as Tc-HYNIC-TOC, ^{111}In-pentetreotide, Ga-DOTATATE, Ga-DOTATOC, and Ga-DOTANOC. Tc-HYNIC-TOC and ^{111}In-pentetreotide require SPECT or SPECT/CT imaging with lower spatial resolution, limiting detection of small lesions. Ga-SSA PET/CT imaging offers improved spatial resolution and signal-to-noise ratio, and Ga-SSA demonstrates higher affinity for somatostatin receptors, significantly improving diagnostic sensitivity. Ga-DOTATATE was FDA-approved in 2016. Therefore, when available, Ga-DOTATATE PET/CT is recommended for somatostatin receptor imaging.

^{1} F-DOPA PET/CT ^{1} F-DOPA is ^{1} F-labeled L-DOPA, a catecholamine synthesis precursor that enters neuroendocrine cells and islet cells via dopamine receptor-mediated transport. Within cells, aromatic L-amino-acid decarboxylase (AADC) decarboxylates L-DOPA to dopamine, making ^{1} F-DOPA uptake a reflection of cellular AADC activity. In pancreatic -cells with robust insulin synthesis and secretion, ^{1} F-DOPA uptake is markedly higher than in normal cells. ^{1} F-DOPA PET and PET/CT are the most effective methods for localizing congenital hyperinsulinemic hypoglycemia (congenital -cell hyperplasia) in infants, distinguishing focal from diffuse -cell hyperplasia to guide surgical planning (partial vs. total pancreatectomy) (44–46).

Unlike infantile congenital hyperinsulinemic hypoglycemia, the diagnostic performance of ^{1} F-DOPA PET and PET/CT for insulinoma in adults (the predominant age group, though rare pediatric cases exist) remains controversial, with reported sensitivities ranging from 17% to 90% (10, 47). This wide variation primarily reflects that while infantile pancreatic exocrine glands contain minimal AADC, allowing predominant -cell uptake, adult pancreatic acinar cells contain very high AADC levels, resulting in predominant acinar uptake that obscures differentiation between insulinoma lesions and normal pancreatic tissue (47). However, recent studies employing pre-examination carbidopa administration to inhibit peripheral AADC activity combined with early dynamic ^{1} F-DOPA PET/CT imaging have achieved sensitivities of 73% (48, 49). Although the diagnostic efficacy of ^{1} F-DOPA for insulinoma requires further clinical validation, current results suggest it may serve as a second-line nuclear medicine imaging method for insulinoma localization.

Conclusion

Nuclear medicine imaging localization methods for insulinoma offer unique functional imaging advantages. GLP-1 receptor imaging (Ga-exendin-4 PET/CT) demonstrates exceptionally high sensitivity and specificity for insulinoma localization and warrants clinical promotion and application. For rare malignant insulinomas, combined somatostatin receptor and GLP-1 receptor imaging repre-

sents an ideal approach for comprehensive disease staging. [1] F-DOPA PET/CT shows promise as a second-line nuclear medicine imaging method for insulinoma localization.

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Note: Figure translations are in progress. See original paper for figures.