Value of ^{68}Ga-DOTATOC and Carbidopa-Assisted ^{18}F-DOPA PET/CT for Insulinoma Localization

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Our objective was to assess the value of ^{68}Ga-DOTATOC and carbidopa-assisted ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA) in 21 hypoglycemic patients. **Methods:** All patients who underwent ^{68}Ga-DOTATOC or carbidopa-assisted ^{18}F-DOPA PET/CT for suspicion of insulinoma from January 2019 to January 2021 were retrospectively analyzed. A final diagnosis of insulinoma was determined by pathologic reports or consensus. **Results:** During the study period, 21 patients underwent both ^{68}Ga-DOTATOC and ^{18}F-DOPA PET/CT. A final diagnosis of insulin-secreting tumor was reached in 12 cases, including 11 insulinomas and 1 small mixed neuroendocrine/nonneuroendocrine neoplasm. ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were positive in 5 (45%) and 7 (64%) of 11 cases, respectively, with 4 concordant positive findings. Moreover, 1 insulinoma was visualized exclusively by ^{18}F-DOPA PET/CT and 3 by ^{68}Ga-DOTATOC PET/CT only. ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were falsely positive in 1 nonfunctioning pancreatic neuroendocrine tumor. **Conclusion:** When ^{68}Ga-exendin-4 is not available, ^{68}Ga-somatostatin receptor PET/CT should be the first choice for insulinoma functional imaging.

Key Words: neuroendocrine tumors; pancreas; insulinoma; ^{18}F-DOPA; ^{68}Ga-DOTATOC

J Nucl Med 2022; 63:384–388
DOI: 10.2967/jnumed.121.262401

In adults, endogenous hyperinsulinemic hypoglycemia is commonly related to insulinoma. Insulinoma can induce severe debilitating and life-threatening hypoglycemia. The average incidence of insulinoma is 1–4 cases per million persons per year, and more than 90% of insulinomas are solitary, sporadic, and benign. In adults with hypoglycemia or suggestive symptoms, the diagnosis of hyperinsulinemic hypoglycemia relies on a positive fasting test (*1*). In 5%–10% of cases, insulinoma can occur in multiple endocrine neoplasia type 1. Parenchyma-sparing (enucleation/pancreatic resection) surgery is the optimal strategy (cure rate, 98%) but can be associated with complications. Accurate localization of insulinoma is therefore of primary importance.

Received Apr. 3, 2021; revision accepted May 27, 2021.
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Published online Jul. 16, 2021.

Imaging work-up of patients with hyperinsulinemic hypoglycemia often requires a combination of anatomic and functional modalities (*2*). ^{68}Ga-exendin-4, which targets the glucagonlike peptide 1 receptor, is expected to become the first-choice radiopharmaceutical for PET detection of benign insulinoma (*3*). However, it is available in only a few centers and is currently used only as a part of clinical trials. A special advantage of ^{68}Ga-exendin-4 over other tracers is its unique value for distinguishing insulinoma from other neuroendocrine tumors—a condition of particular interest in the setting of multiple endocrine neoplasia type 1 patients, who often present with concomitant functioning and nonfunctioning pancreatic tumors. When ^{68}Ga-exendin-4 is not available for clinical use, either ^{68}Ga-radiolabeled somatostatin analog (^{68}Ga-DOTA-SSA) or ^{18}F-fluorodihydroxyphenylalanine (^{18}F-DOPA) can be used (*4*). ^{68}Ga-DOTA-SSA showed encouraging preliminary results for insulinoma imaging in 2 retrospective studies (*5*,*6*). However, insulinoma detection remains challenging, mainly because these tumors have a limited somatostatin receptor (SSTR) 2 expression profile and a small size and because of the physiologically high ^{68}Ga-DOTA-SSA uptake in the uncinate process (*7*). On the other hand, the value of ^{18}F-DOPA PET/CT is hampered by the relatively short duration of ^{18}F-DOPA tumor retention in insulinoma and the diffuse uptake in normal pancreatic parenchyma, which may potentially mask insulinoma (*8*). To circumvent these major drawbacks, we previously proposed a revised imaging protocol based on a dual-phase imaging acquisition and patient premedication with carbidopa (a peripheral aromatic amino acid decarboxylase inhibitor) to prevent physiologic pancreatic ^{18}F-DOPA uptake (*9*).

Currently, there remains a degree of uncertainty regarding the optimal first-choice tracer for patients in whom insulinoma is suspected in the absence of ^{68}Ga-exendin-4. The aim of the present study was to describe the value of ^{68}Ga-DOTA-SSA and carbidopa-assisted ^{18}F-DOPA in a retrospective series of hypoglycemic patients evaluated by both tracers.

MATERIALS AND METHODS

Patients

This retrospective study was conducted in the departments of nuclear medicine of 3 university hospitals in France (Strasbourg, Marseille, and Nancy). We performed a comprehensive search of our databases to identify all patients evaluated by ^{68}Ga-DOTA-SSA or

carbidopa-assisted ^{18}F-DOPA PET/CT for clinical, biologic, or radiologic suspicion of insulinoma-related hyperinsulinemic hypoglycemia from January 2019 to January 2021 (Fig. 1). Of the patients who underwent ^{18}F-DOPA and ^{68}Ga-DOTA-SSA PET/CT, only those studied within a 3-mo period without therapeutic intervention or a change in therapy between the 2 PET studies were included. All data (clinical, biologic, and imaging) were extracted from institutional medical data files (Table 1). The institutional review board approved this retrospective study, and the requirement to obtain informed consent was waived.

Imaging Protocols

All examinations were performed by combined PET/CT devices equipped with 3-dimensional time-of-flight technology. The patients were injected with a 2–3 MBq/kg dose of ^{68}Ga-DOTATOC and a 3–4 MBq/kg dose of ^{18}F-DOPA (2 h after carbidopa premedication, 200 mg orally) without fasting beforehand. ^{68}Ga-DOTATOC PET/CT included a whole-body acquisition from the upper thigh to the top of the skull (3–5 min/step), starting 60 min after radiotracer injection. Dual-time-point ^{18}F-DOPA PET/CT included an early scan of the upper abdomen (at 5 min, 10 min/step) and a delayed whole-body acquisition (at 30 min, 3–5 min/step). In all cases, low-dose nonenhanced CT was performed and used for attenuation correction.

A pancreatic abnormality was defined as a focal area of increased uptake compared with surrounding tissue, considering potential pitfalls for both tracers. For ^{18}F-DOPA PET/CT, a positive early phase followed by a negative delayed scan was considered a pathologic study. Semiquantitative analysis was performed by centering a spheric volume of interest on the uptake foci.

Gold Standard

The final diagnosis of insulinoma was determined by the pathologic results when available. In the remaining patients, the diagnosis was reached by a consensus considering clinical, biologic (positive fast test), and radiologic (CT/MRI typical enhancement) parameters and follow-up.

Statistical Analysis

The results for continuous data are expressed as the mean ± SD or the median and range as appropriate, whereas categoric variables are presented as numbers and percentages. Detection rate, sensitivity, and specificity are provided for both modalities.

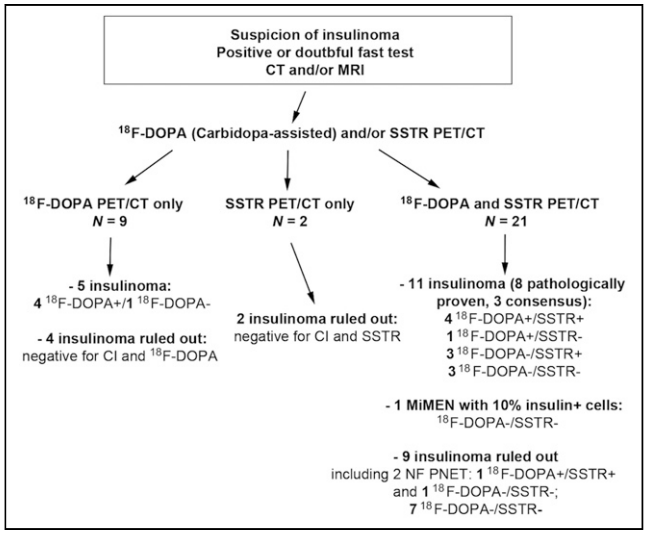

FIGURE 1. Flowchart summarizing study design and key PET/CT imaging findings. MiMEN = mixed neuroendocrine–nonneuroendocrine neoplasm; NF = not functioning.

RESULTS

Patient Population

In total, 32 patients were evaluated during the study period: 9 with ^{18}F-DOPA PET/CT alone, 2 with only ^{68}Ga-DOTATOC PET/CT, and 21 with both tracers (Fig. 1). The 21 patients imaged with both tracers constituted the study population. The patients' characteristics are summarized in Table 1.

Fourteen of 21 patients had a positive 72-h fasting test, whereas 7 had doubtful results. In patients with borderline biochemical and imaging findings, the indication for further evaluation was decided in the setting of institutional multidisciplinary meetings.

A final diagnosis of an insulin-secreting tumor was reached in 12 patients, including 11 insulinomas (1 occult) and 1 small mixed neuroendocrine/nonneuroendocrine neoplasm with 15% insulin cell positivity. Among them, the fasting test was positive in 10 patients and inconclusive in the remaining 2 patients. Among the 11 insulinomas, 8 were pathologically proven; among the other 3 cases, the diagnosis was reached by consensus. In 7 patients without a detectable pancreatic target lesion on either anatomic and functional imaging, the diagnosis of insulinoma was excluded by follow-up. In the other 2 patients, the diagnosis turned out to be nonfunctioning pancreatic neuroendocrine tumors confirmed by surgery or endoscopic ultrasound-guided fine-needle aspiration biopsy and follow-up.

PET/CT Findings

The PET/CT findings are summarized in Figure 1. For insulinoma, ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were positive in 5 and 7 of the 11 patients, respectively, with concordant positive findings in 4 patients. Moreover, 1 insulinoma was visualized exclusively by ^{18}F-DOPA PET/CT, and 3 were visualized only by ^{68}Ga-DOTATOC PET/CT (Fig. 2). On ^{18}F-DOPA PET/CT, delayed-phase imaging failed to detect 1 insulinoma that was correctly identified by early-phase ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT (Fig. 2). In this patient, the insulinoma was related to multiple endocrine neoplasia type 1 syndrome, and the patient had a previous history of 3 benign insulinomas that were positive on somatostatin receptor scintigraphy and successfully treated by surgery. In the other patients, insulinomas were sporadic. One 10-mm grade 1 mixed neuroendocrine–nonneuroendocrine neoplasm remained occult on both ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT, likely because of the small percentage of the neuroendocrine component.

Among 2 patients with nonfunctioning pancreatic neuroendocrine tumors, ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT were falsely positive in one and negative in the other. The diagnosis of insulinoma was excluded in 7 additional patients without identifiable pancreatic target images on either PET imaging study. The overall detection rate, sensitivity, and specificity were, respectively, 45%, 42%, 89% for ^{18}F-DOPA and 64%, 58%, 89% for ^{68}Ga-DOTATOC PET/CT.

The tumor-to-background uptake ratios were more favorable with ^{68}Ga-DOTATOC than with ^{18}F-DOPA PET. The mean ratios of tumor SUV_{max} and tumor SUV_{max} to normal pancreas SUV_{mean} were 6.7 and 1.5, respectively, for early-phase ^{18}F-DOPA; 6.3 and 2.7, respectively, for delayed-phase ^{18}F-DOPA; and 45.2 and 10.8, respectively, for ^{68}Ga-DOTATOC PET/CT.

TABLE 1
Patients with Suspected Insulinoma Who Underwent Both Carbidopa-Assisted ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT

Patient no.	Age (y)	Sex	24-h fast test	Medical treatment	CT/MRI	EUS	Early/delayed ^{18}F-DOPA/ SSTR PET/CT	Final diagnosis	Gold standard
1	62	F	Positive	Diazoxide	+/+, head	+, head	+/+/+, head	Insulinoma, 10-mm, grade 1, Ki-67: 2%	Pathology (surgery)
2	31	F	Doubtful	Diazoxide	−/−	?, body	−/−/−	Insulinoma excluded	Consensus
3	16	F	Positive	Diazoxide	−/−	—	−/−/−	Insulinoma excluded	Consensus
4	70	M	Positive	Diazoxide	+/+, tail		+/+/+, tail	Nonfunctioning pNET, 66-mm, grade 3, Ki-67: 25%	Pathology (surgery)
5	19	F	Positive		−/−		−/−/−	Insulinoma excluded	Consensus
6	62	F	Positive		+/NA, body	+, body	−/−/+, body	Insulinoma, 17-mm	Pathology (FNAB)
7	71	F	Doubtful		−/NA	−	+/+/+, head	Insulinoma, 18-mm, grade 1, Ki-67: 1%	Pathology (surgery)
8	77	F	Doubtful		−/−	?, tail	−/−/−	Insulinoma excluded	Consensus
9	65	M	Positive		−/−	+, body	−/−/−	MiNEN, 10-mm, grade 1 (IHC: 15% insulin-positive, 90% SST-positive)	Pathology (surgery)
10	48	F	Positive		+/+, tail		+/+/+, tail	Insulinoma, 17-mm, grade 1, Ki-67: 1%	Pathology (surgery)
11	78	F	Positive	Diazoxide	+/NA, tail		−/−/−	Insulinoma, 12-mm, grade 1, Ki-67: 2%	Pathology (surgery)
12	64	F	Positive		−/−		−/−/−	Insulinoma excluded	Consensus
13	27	F	Doubtful		+/+, head		+/−/+, head	Insulinoma, 10-mm (MRI)	Consensus
14	64	M	Doubtful		−/−		−/−/−	Insulinoma excluded	Consensus
15	78	F	Doubtful		−/NA		−/−/−	Insulinoma excluded	Consensus
16	29	F	Positive		−/+, tail		+/+/−, tail	Insulinoma, 12-mm, grade 1, Ki-67: 1%	Pathology (surgery)
17	67	F	Positive	Diazoxide	−/−	−	−/−/−	Insulinoma (occult)	Consensus
18	64	F	Doubtful		−/+, body	+, body	−/−/−	Nonfunctioning pNET, 5-mm, grade 1, Ki-67: 1%	Pathology (FNAB)
19	72	M	Positive	Diazoxide	+/NA, head	+	−/−/+, head	Insulinoma, 10-mm	Pathology (FNAB)
20	93	M	Positive	Diazoxide	+/NA, tail	−	−/−/+, tail	Insulinoma, 13-mm	Consensus
21	52	M	Positive		NA/+, head	+, head	−/−/−	Insulinoma, 22-mm	Pathology (FNAB)

EUS = endoscopic ultrasound; + = positive result; − = negative result; ? = doubtful result; pNET = pancreatic neuroendocrine tumor; NA = not available; FNAB = fine-needle aspiration biopsy; MiNEN = mixed neuroendocrine–nonneuroendocrine neoplasm; IHC = immunohistochemistry.

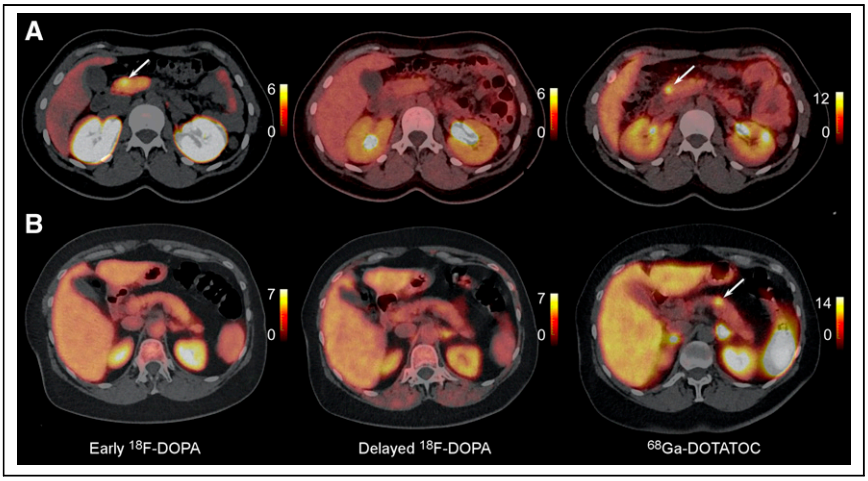

FIGURE 2. Discordant results for carbidopa-assisted ^{18}F-DOPA and ^{68}Ga-DOTATOC PET/CT in 2 patients with pathologically proved insulinoma (arrows). (A) Early ^{18}F-DOPA–positive/delayed ^{18}F-DOPA–negative/^{68}Ga-DOTATOC–positive findings. (B) Early ^{18}F-DOPA–negative/delayed ^{18}F-DOPA–negative/^{68}Ga-DOTATOC–positive findings.

DISCUSSION

The present study aimed to describe the value of ^{68}Ga-SSTR PET/CT and carbidopa-assisted ^{18}F-DOPA in a series of hypoglycemic patients. The principal conclusions were, first, that ^{68}Ga-DOTATOC PET/CT has a high detection rate in insulinoma, although its value is less than that in nonfunctioning pancreatic neuroendocrine tumors because of a lack of SSTR2 expression in a subgroup of insulinomas (*10*), and, second, that ^{68}Ga-DOTATOC PET/CT can be positive when ^{18}F-DOPA fails (3 cases) and vice versa (1 case). The latter point is easily comprehensible because of the various molecular determinants of tracer uptake and retention in both conditions.

Although our study was not designed to perform a reliable comparison between ^{68}Ga-SSTR PET/CT and ^{18}F-DOPA (mainly because the study was retrospective and had a limited number of patients), we suggest using ^{68}Ga-SSTR PET as the first-choice tracer when ^{68}Ga-exendin-4 is not available. This position could be supported by several arguments. Two recent retrospective studies showed promising results concerning the use of ^{68}Ga-SSTR PET/CT in patients with insulinoma-related hyperinsulinemic hypoglycemia, allowing for the identification of pancreatic secreting tumors in 9 of 10 (90%) and 11 of 13 patients (85%) (*5*,*6*). The greater sensitivities described in these studies than in our study could be related to the inclusion of solely pathologically proven insulinomas (*5*,*6*), excluding patients with nonoperated ^{68}Ga-SSTR–negative insulinoma. Furthermore, on the basis of the widely admitted expression of SSTR2 in two thirds of insulinomas (*10*), it is expected that ^{68}Ga-SSTR PET/CT sensitivity in real-life situations should be less than previously reported, with an on–off uptake pattern, depending on SSTR2 expression. The use of ^{68}Ga-SSTR PET/CT also has practical advantages over ^{18}F-DOPA in terms of availability and cost for teams skilled and suitably equipped for ^{68}Ga radiolabeling.

Although the application of carbidopa-assisted ^{18}F-DOPA PET/CT remains controversial (*11*), the present study showed that it can be useful for SSTR-negative insulinoma and therefore can be considered a second-choice tracer when ^{68}Ga-SSTR PET/CT fails to detect the tumor. The lower rate of ^{18}F-DOPA PET/CT positivity than previously reported could also be related to selection bias. As highlighted in the flowchart, 5 insulinomas, including 4 with ^{18}F-DOPA–positive findings, did not undergo ^{68}Ga-SSTR PET/CT. With these patients, the rate of positivity would therefore be 56% (9/16). Physicians should be aware that imaging protocols should be adapted, including carbidopa premedication. We previously showed in a preclinical model that the use of carbidopa did not inhibit insulinoma ^{18}F-DOPA uptake (*12*), a phenomenon that was described for β-cell hyperplasia (*13*). In the present study, delayed acquisition missed 1 insulinoma, and early acquisition was never inferior to delayed acquisition. In a previous study that included 24 patients, 4 cases were detected only by early-phase acquisition (*14*).

CONCLUSION

Despite the limitations that have been pointed out, this study provided new data on both tracers in this rare but curable disease. When ^{68}Ga-exendin-4 is not available, we suggest using SSTR analogs as the first-choice PET tracer and considering carbidopa-assisted ^{18}F-DOPA as a valid alternative when the results are inconclusive.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the best radiopharmaceutical for insulinoma localization in the absence of ^{68}Ga-exendin-4?

PERTINENT FINDINGS: When ^{68}Ga-exendin-4 is not available, ^{68}Ga-SSTR should be considered the first-choice PET tracer. Carbidopa-assisted ^{18}F-DOPA PET remains a valid option when the results are inconclusive.

IMPLICATIONS FOR PATIENT CARE: ^{68}Ga-SSTR PET/CT enables detection of insulinoma, allowing curative sparing surgery (enucleation/pancreatic resection) and resolution of preoperative symptoms.

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