Clinical Value of $^{18}$F-FDOPA PET/CT With Contrast Enhancement and Without Carbidopa Premedication in Patients with Insulinoma

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Abstract. Aim: We evaluated the clinical usefulness of $^{6}$-$^{18}$F-fluoro-3,4-dihydroxy-L-phenylalanine($^{18}$F-FDOPA)-positron-emission tomography (PET)/computed tomography (CT) in insulinoma detection with contrast enhancement, early acquisition time, and no carbidopa premedication. Patients and Methods: Twenty-six patients diagnosed with hyperinsulinemic hypoglycemia underwent an $^{18}$F-FDOPA PET/CT examination. Patients without carbidopa premedication and contrast-enhanced CT were included. Imaging findings were compared to the overall final diagnosis (histological findings). Results: In 10 of 26 patients (eight women, two men; mean age=53 years; age range=30-94 years), a detected lesion was confirmed histologically as an insulinoma. $^{18}$F-FDOPA PET detected the tumor in five out of ten patients. Contrast-enhanced CT also detected the tumor in five out of ten. Overall, $^{18}$F-FDOPA PET/CT, with contrast enhancement and without carbidopa premedication, was able to detect the insulinoma in seven out of ten patients (70%). Conclusion: Based on our data, $^{18}$F-FDOPA PET/CT, with contrast enhancement and without carbidopa premedication, as a 'one-stop' diagnostic modality is a viable option for insulinoma detection.

In adults, the rare tumor known as an insulinoma is the most common cause of hyperinsulinemic hypoglycemia (HH), which is usually sporadic, unique, and benign, although 10% are malignant (1-4). The localization of an insulinoma is a challenge for conventional diagnostic modalities, such as computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS). In recent years, functional imaging modalities have gained momentum in clinical practice.

Positron-emission tomography (PET) imaging, using $^{68}$Ga-labeled somatostatin analogs, has been introduced for the imaging of neuroendocrine tumors (NET), but to date, its sensitivity in imaging of insulinomas is largely unknown, with disappointing preliminary results (5). The use of radiolabeled glucagon-like peptide-1 (GLP1) analogs have shown promising results (6-8). This is due to the high expression of GLP1 receptors in insulinomas (9) and normal GLP1 receptor expression in pancreatic tissue, even in patients with post-gastric bypass hypoglycemia (10). These tracers have not yet, however, found widespread use due to the lack of commercially available kits and the need for on-site radiopharmaceutical synthesis (11).

$^{6}$-$^{18}$F-fluoro-3,4-dihydroxy-L-phenylalanine ($^{18}$F-FDOPA) has been proposed as a useful radiopharmaceutical for the imaging of catecholamine-secreting tumors. In particular, a few studies have described the clinical value of $^{18}$F-DOPA in the detection of insulinoma (12-14).

Carbidopa is an inhibitor of the peripheral aromatic amino acid decarboxylase and may improve interpretation of $^{18}$F-FDOPA-PET by significantly increasing tumor uptake while lowering physiological pancreatic uptake (15, 16).

The published data relating to the clinical value of $^{18}$F-FDOPA-PET in patients with insulinoma is very limited, inconsistent (different acquisition PET protocols with or without CT attenuation, carbidopa premedication), and involves small cohorts. It should be emphasized that contrast-enhanced CT is a very important part of the diagnosis of insulinoma, since pancreatic NETs absorb the contrast agent in the arterial phase of the imaging procedure.

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and thus, CT allows the detection of a lesion in the pancreas. Nevertheless, the potential diagnostic benefit of a contrast enhanced CT component was not utilized in these studies (12-14).

At our Department, in patients with HH and suspected insulinoma, \(^{18}\)F-FDOPA-PET/CT with contrast enhancement, early acquisition time, and no carbidopa-premedication was performed. In the present study, we evaluated the clinical usefulness of \(^{18}\)F-FDOPA-PET/CT with the above-mentioned conditions that would make this method a ‘one-stop’ examination.

**Patients and Methods**

**Patients.** In this retrospective study, the detection rate in patients with HH who were referred to our Department between January 2010 and August 2015 for imaging of clinically suspected insulinoma was studied. All patients underwent a pre-treatment \(^{18}\)F-FDOPA PET/CT examination.

The study was approved by the local Ethics Committee (approval number: 1015/2016).

**Imaging.** For all patients, a whole-body PET/CT examination (i.e. from the head to the upper thigh) was performed using a Siemens Biograph 64-row, multi-detector, hybrid PET/CT system (Siemens, Erlangen, Germany). The PET tracer \(^{18}\)F-FDOPA was commercially obtained from IASON (Graz, Austria). None of the patients received carbidopa premedication.

The CT protocol included a whole-body, contrast-enhanced (post-injection delay, 16 s and 65 s) series, which was obtained following intravenous injection of 120 ml of a tri-iodinated, non-ionic contrast medium (Iomeron 300; Bracco, Milan, Italy) at the rate of 4 ml/s, followed by a 50-ml saline flush. CT images of all series were reconstructed with a soft-tissue kernel (B30f), using the following CT acquisition parameters: tube voltage, 120 mAs; tube current, 230 kV; collimation, 64×0.6 mm; reconstruction orientation, transverse; reconstruction section thickness, 3 mm with 2-mm increments; matrix, 512×512. The CT data were acquired during suspended expiration. Without changing the patient’s position, PET images were obtained approximately 20 min following the intravenous administration of 250 MBq \(^{18}\)F-DOPA. The PET was performed over five to six bed positions for 3 min/bed position. PET images were reconstructed using the TrueX algorithm (Siemens, Erlangen, Germany), with four iterations per 21 subsets, a matrix size of 168×68, and a slice thickness of 5 mm. The attenuation correction was based on the CT maps. All CT and PET data were co-registered, and fused, color-coded PET/CT images were generated. Maximum tissue standardized uptake values (SUV\(_{\text{max}}\)) were based on elliptic regions of interest manually drawn around lesions of \(^{18}\)F-FDOPA uptake.

**Image interpretation.** Physicians who were experienced in nuclear medicine and radiology interpreted the images of all patients. The readers were blinded to the identity and history of the patients, the specific indication (primary search, staging in malignant history), the histological and radiological reports, as well as to the clinical history. In the first session, CT and PET images were reviewed independently, in random order. CT was evaluated on a Picture Archiving and Communication System workstation, whereas PET images were evaluated using a Syngo Multi-Modality workstation (Siemens, Erlangen, Germany) using a TrueD software module. On CT, a lesion was rated as an insulinoma if the characteristic strong contrast enhancement was present. On PET, a lesion was rated as an insulinoma if \(^{18}\)F-FDOPA uptake was increased compared to the surrounding pancreatic tissue (visual criterion).

After a time interval of 6 weeks, PET/CT images were evaluated in consensus, in a different, randomized sequence, taking into account the above-described PET and CT criteria. A lesion was rated as an insulinoma if the PET was positive, or if the PET was negative but the lesion showed a strong contrast enhancement.

For further analysis, imaging findings were compared to the overall final diagnosis. Final diagnosis was established only by histological findings of surgically proven lesions (reference standard).

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**Table I. Demographic data and results of the respective imaging modality.**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Gender</th>
<th>Age, years</th>
<th>(^{18})F-FDOPA PET</th>
<th>CE-CT</th>
<th>Concordant PET/CT</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>f</td>
<td>29</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>39</td>
<td>−</td>
<td>+</td>
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<tr>
<td>3</td>
<td>f</td>
<td>89</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>4</td>
<td>f</td>
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<td>+</td>
<td>−</td>
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</tr>
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<td>m</td>
<td>40</td>
<td>+</td>
<td>+</td>
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<td>+</td>
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<tr>
<td>6</td>
<td>f</td>
<td>27</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>33</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>f</td>
<td>72</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>9</td>
<td>f</td>
<td>39</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>10</td>
<td>f</td>
<td>61</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Total</td>
<td>8 f/2 m</td>
<td>50±21*</td>
<td>5 +/5 −</td>
<td>5 +/5 −</td>
<td>3 +/7 −</td>
<td>7 +/3 −</td>
</tr>
</tbody>
</table>

f: Female, m: male, \(^{18}\)F-FDOPA: 6-[\(^{18}\)F]-fluoro-3,4-dihydroxy-L-phenylalanine, PET: positron-emission tomography, CE-CT: contrast enhanced computed tomography. *Mean±standard deviation.
Statistical analysis. The sensitivity for our imaging procedure was calculated. Furthermore, the mean and standard deviation were calculated for SUV\textsubscript{max} and SUV\textsubscript{mean} and unpaired \textit{t}-tests were used to compare healthy and tumorous tissue. A two-sided value of \( p \leq 0.05 \) was considered a statistically significant result.

Results

Within our cohort, all 26 patients with HH and suspected insulinoma underwent a whole-body \(^{18}\text{F}-\text{FDOPA PET/CT} \) examination. Ten out of these 26 patients met our inclusion criteria (contrast-enhanced CT, early acquisition, no carbidopa-premedication, histologically verified insulinoma). Table I shows the demographic data and the results of the respective imaging modality. Eight patients were initially admitted for hypoglycemia of unknown origin, one patient for syncope and another for vertigo and other neurological symptoms. A positive fasting test was performed in all patients.

Of the 16 patients excluded from final analysis, the final diagnosis was dumping syndrome in four cases; autoimmune hypoglycemia in one case; diffuse nesidioblastosis in one case; non specified NET of the pancreas (surgery was performed at a different site) in one case; gastrin-producing NET with a small insulin-producing portion in one case; metastasized insulinoma with hepatic metastases where no primary tumor mass was found in one case; and suspected insulinoma in one case where the tumor was inoperable due to anatomical location. In five cases, no clear diagnosis was made. \(^{18}\text{F}-\text{DOPA PET} \) was positive in none of these cases, contrast-enhanced CT was positive in the case of the non-specified NET and inoperable suspected insulinoma.

Five patients (numbers 1, 3, 4, 5 and 10) had a positive result on \(^{18}\text{F-FDOPA PET} \), with three insulinomas in the head of the pancreas and two in the tail. Five patients (numbers 2, 3, 5, 7 and 10) had a positive result on contrast-enhanced CT, with three insulinomas in the pancreatic head and one each in both the body and tail. Three patients (numbers 3, 5 and 10) had concordant results on \(^{18}\text{F-FDOPA PET} \) and contrast-enhanced CT (Figure 1). Three patients (numbers 6, 8 and 9) had negative results by both modalities.

The SUV\textsubscript{max} for \(^{18}\text{F-FDOPA-PET-positive patients} \) was calculated. For patients with negative results in the \(^{18}\text{F-FDOPA-PET} \), a descriptive SUV\textsubscript{mean} for the whole pancreas was obtained (Table II). SUV\textsubscript{max} and SUV\textsubscript{mean} for the insulinoma location and healthy pancreatic tissue was compared for the two patients (numbers 02 and 07) with positive contrast-enhanced CT and negative \(^{18}\text{F-FDOPA-PET} \). Patient 2 had an SUV\textsubscript{max} of 2.14 and an SUV\textsubscript{mean} of 1.09 compared to a SUV\textsubscript{max} of 2.15 and a SUV\textsubscript{mean} of 1.51 in healthy pancreatic tissue. Patient 7 similarly had a SUV\textsubscript{max} of 6.56 and a SUV\textsubscript{mean} of 6.13 compared to a SUV\textsubscript{max} of 6.63 and a SUV\textsubscript{mean} of 5.75 in healthy pancreatic tissue.

The final results showed that \(^{18}\text{F-FDOPA-PET/CT} \), in accordance with our image evaluation criteria, was able to detect seven out of 10 histologically-verified insulinomas in patients with HH (sensitivity 70%). \(^{18}\text{F-FDOPA PET} \) without carbidopa premedication was able to detect five out of 10 (sensitivity 50%) tumors, and contrast-enhanced CT five out
of 10 tumors (sensitivity 50%). The SUVmax values for our five 18F-FDOPA PET-positive patients ranged from 4.99 to 19.86, with an SUVmean value of 12.85±5.86. The SUVmean values of healthy pancreatic tissue of all 10 patients ranged from 1.51 to 8.82, with a mean value of 5.64±1.98. The unpaired t-test, with regard to pathological tumor tissue and normal tissue in the pancreas (SUVmax & mean), gave a p-value of 0.015, and was, therefore, considered statistically significant.

Discussion

In this retrospective study, we evaluated our imaging protocol for the detection of insulinoma using 18F-FDOPA PET/CT. With no carbidopa premedication, an acquisition time of 20 min, and the additional implementation of contrast-enhanced CT, our protocol functions as a ‘one-stop’ hybrid imaging modality. We decided not to include carbidopa premedication, in contrast to recommendations proposed by Imperiale et al. (14) because 18F-FDOPA PET/CT without premedication has not been examined using an early acquisition protocol. In addition, a masking effect of carbidopa on tumor uptake has been reported in case studies (17), and insulinomas with low aromatic amino acid decarboxylase expression may be potentially more sensitive to carbidopa inhibition (18). In previously published studies, all patients had already undergone contrast-enhanced CT at the time of 18F-FDOPA PET/CT examination (12-14). We wanted to examine the diagnostic benefit of implementing a ‘one-stop’ protocol using this hybrid imaging modality.

Our overall results compare favorably to previously published studies. The initially reported sensitivity of 90% for insulinoma in non-attenuation-corrected 18F-FDOPA PET with an acquisition time of 60 min by Kauhanen et al. (12) could not be reproduced in any subsequent study. However, our early acquisition protocol led to a better 18F-FDOPA PET sensitivity than was reported by Tessonnier et al., who used acquisition times of 1 h or more (13). The overall pooled sensitivity of our hybrid imaging protocol led to a sensitivity of 70%, which is similar to the 73% sensitivity found by Imperiale et al. using carbidopa premedication and an acquisition time of 5 min (14). It is of note that Imperiale et al. used a dual time acquisition protocol with a delayed acquisition time of 20 to 30 min. In these delayed images, only five out of 11 (45% sensitivity) were PET-positive, which is similar to our results at an acquisition time of 20 min (14).

Interestingly, our data suggest only a modest concordance between PET imaging and contrast-enhanced CT, making both modalities important for the diagnosis of insulinoma and supports our ‘one-stop’ approach.

In a recent study, Detour et al. examined 18F-FDOPA accumulation in an insulinoma xenograft model in mice with carbidopa premedication. Murine β-cell line RIN-m5F was used to assess in vitro accumulation. In vivo small-animal PET experiments were performed on tumor-bearing nude mice after subcutaneous injection of RIN-m5F cells. With carbidopa premedication, there was no evidence of in vitro 18F-FDOPA accumulation in RIN-m5F cells and in vivo imaging was improved (19). These findings suggest that carbidopa can be used to inhibit uptake in healthy pancreatic tissue without concern about masking lesions.

GLP1 analogs have recently been shown to possess great sensitivity in the detection of insulinomas (20, 21). Furthermore, in a prospective multicentric study conducted by Christ et al., using 111In-diethylenetriaminepentaacetic acid-exendin-4 for single-photon-emission CT examination, a transient exacerbation of hypoglycemia was reported (20). A large, prospective cohort study by Luo et al., using 68Ga-labeled exendin-4 derivative, also showed promising sensitivity for PET/CT when compared to other imaging modalities. High uptake in the kidneys, however, necessitated further imaging 2 to 3 h after injection in some cases (21).

In two recent studies, Prasad et al. (22) and Nockel et al. (23) re-evaluated the diagnostic value of two somatostatin analog tracers 68Ga-DOTA-(Tyr3)-octreotate and 68Ga-dostreotide in insulinoma detection. With cohorts of 13 (although Prasad et al. included patients with nesidioblastosis in their cohort) and 10 patients, these studies showed a sensitivity of somatostatin receptor PET/CT of 84.7% and 90%, respectively (22, 23).

We acknowledge the limitations of this study: its retrospective design and the understandably small cohort.
Based on our findings and the review of the literature, further study is needed to evaluate the positive or negative effect of carbidopa premedication on the detection of insulinoma. With the same acquisitio time, our results without carbidopa premedication compare very favorably to those found by Imperiale et al. (sensitivity of 50% vs. 45%, respectively) (14). The modest concordance between 18F-FDOPA PET and contrast-enhanced CT suggests a diagnostic benefit of the implementation of contrast enhancement in order to maximize diagnostic efficacy.

Conclusion

This study represents a retrospective evaluation of the viability of 18F-FDOPA PET without carbidopa premedication in combination with contrast-enhanced CT as a ‘one-stop’ examination. Our imaging procedure and evaluation was useful in 7 out of 10 patients with histologically-verified insulinoma, and required a single visit to our hospital to reach a final diagnosis. Our own procedure is also not an optimal modality, but, compared to other established modalities, it is not inferior and carries a similar level of sensitivity. Further studies must focus on a unified imaging procedure with regard to the choice of whether to use contrast-enhanced CT with 18F-FDOPA PET scan when using carbidopa premedication.

Compliance with Ethical Standards

This study was approved by the local Ethics Committee, and, for this retrospective type of study, informed consent of patients was not required.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in regard to this study.

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