Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study

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Summary

Background **Small benign insulinomas are hard to localise, leading to difficulties in planning of surgical interventions. We aimed to prospectively assess the insulinoma detection rate of single-photon emission CT in combination with CT (SPECT/CT) with a glucagon-like peptide-1 receptor avid radiotracer, and compare detection rates with conventional CT/MRI techniques.**

Methods **In our prospective imaging study, we enrolled adults aged 25–81 years at centres in Germany, Switzerland, and the UK. Eligible patients had proven clinical and biochemical endogenous hyperinsulinaemic hypoglycaemia and no evidence for metastatic disease on conventional imaging. CT/MRI imaging was done at referring centres according to standard protocols. At three tertiary nuclear medicine centres, we used whole body planar images and SPECT/CT of the abdomen up to 168 h after injection of ^{111}In-[Lys$_{40}$(Ahx-DTPA-^{111}In)NH$_2$]-exendin-4 (^{111}In-DTPA-exendin-4) to identify insulinomas. Consenting patients underwent surgery and imaging findings were confirmed histologically.**

Findings **Between Oct 1, 2008, and Dec 31, 2011, we recruited 30 patients. All patients underwent ^{111}In-DTPA-exendin-4 imaging, 25 patients underwent surgery (with histological analysis), and 27 patients were assessed with CT/MRI. ^{111}In-DTPA-exendin-4 SPECT/CT correctly detected 19 insulinomas and four additional positive lesions (two islet-cell hyperplasia and two uncharacterised lesions) resulting in a positive predictive value of 83% (95% CI 62–94). One true negative (islet-cell hyperplasia) and one false negative (malignant insulinoma) result was identified in separate patients by ^{111}In-DTPA-exendin-4 SPECT/CT. Seven patients (23%) were referred to surgery on the basis of ^{111}In-DTPA-exendin-4 imaging alone. For 23 assessable patients, ^{111}In-DTPA-exendin-4 SPECT/CT had a higher sensitivity (95% [95% CI 74–100]) than did CT/MRI (47% [27–68]; p=0·011).**

Interpretation **^{111}In-DTPA-exendin-4 SPECT/CT could provide a good second-line imaging strategy for patients with negative results on initial imaging with CT/MRI.**

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Introduction

Benign insulinomas are small neuroendocrine tumours that are nearly always located in the pancreas and are the most common cause of endogenous hyperinsulinaemic hypoglycaemia in adult patients without diabetes.[1] Conventional imaging (ie, CT/MRI) and, if available, endoscopic ultrasound form the basis of localisation and diagnosis of suspected insulinoma.[2–5] However, because of the small size of these tumours, localisation with conventional procedures has notable diagnostic difficulties.[6] Methods such as selective intra-arterial calcium stimulation and venous sampling (ASVS) have a better sensitivity than do conventional techniques, but are invasive procedures with a concomitant risk of complications.[6–8]

As somatostatin receptor expression is low in benign insulinomas,[9] detection rates with somatostatin receptor scintigraphy are low, and thus development of a new receptor targeted imaging technique for this type of neuroendocrine tumour will be important. Data from in-vitro studies suggest that benign insulinomas have a very high density of glucagon-like peptide-1 receptors (GLP-1R) that might be used as specific targets for in-vivo receptor imaging.[10]

GLP-1 or its analogues, liraglutide and exenatide, enhance insulin secretion by β cells and have been introduced for treatment of type 2 diabetes.[11,12] Several GLP-1-like radioligands retaining high binding affinity to GLP-1R have been developed, including the specific ligand [Lys^{40}(Ahx-DOTA)NH$_2$]exendin-4 and [Lys^{40}(Ahx-DTPA)NH$_2$]exendin-4 labelled with indium-111 (^{111}In-DOTA-exendin-4 and ^{111}In-DTPA-exendin-4) and [Lys^{40}(Ahx-HYNIC)NH$_2$]exendin-4 labelled with technetium-99m (^{99m}Tc-HYNIC-exendin-4).[13–17] In a proof-of-principle study,[18] ^{111}In-DOTA-exendin-4 was given to six patients with endogenous hyperinsulinaemic hypoglycaemia. Single-photon emission CT in combination with CT (SPECT/CT) detected the lesion in all six patients whereas conventional imaging appropriately located the tumour in only one patient and endosonography was positive in four

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See Comment page 82

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patients. Notably, in-vitro GLP-1R autoradiography of the surgical specimen showed a high density of GLP-1R in all six insulinomas.[18] Similarly, ^{99m}Tc-HYNIC-exendin-4 showed promising results in a recent report.[15]

A curative treatment approach for insulinoma relies on surgical removal of the tumour. Therefore, identification of the precise preoperative location of the insulinoma is crucial to reduce the extent of the surgical intervention and allow for preservation of pancreatic tissue.[3,6] The results of the proof-of-principle study[18] showed that GLP-1R imaging is capable of localising insulinomas in vivo.

See Online for appendix

Our study aimed to determine the insulinoma detection rates of ^{111}In-DTPA-exendin-4 SPECT/CT and conventional imaging, and to assess whether ^{111}In-DTPA-exendin-4 SPECT/CT changes clinical management in patients with negative conventional imaging.

Methods

Study design and patients

In our prospective multicentre imaging study, we screened patients with suspected hyperinsulinaemic hypoglycaemia (positive Whipple triad) at tertiary referral centres in Switzerland (University of Basel Hospital, University of Berne Hospital, Kantonsspital Lucerne, and Kantonsspital St Gallen), Germany (University Hospital Freiburg), and the UK (Royal Free Hospital) according to the present guidelines.[19] We enrolled adults aged 25–81 years with biochemically proven endogenous hyperinsulinaemic hypoglycaemia in the fasting state (ie, neuroglycopenic symptoms in the fasting state with low plasma glucose, inappropriately high serum insulin and C-peptide concentrations, and a negative screening for sulfonylurea).[20] In addition, to exclude patients with evidence of malignant insulinoma, local conventional imaging (CT/MRI) had to have shown no or only one suspicious lesion. We excluded pregnant women, patients with allergies to exendin-4, and patients with renal insufficiency (blood creatinine concentrations >140 µmol/L). All patients who fulfilled inclusion criteria (reviewed by EC) were referred to one of the three tertiary nuclear medicine referral centres (University of Basel Hospital, Basel, Switzerland; University Hospital Freiburg, Freiburg, Germany; University College London Hospital, London, UK) for ^{111}In-DTPA-exendin-4 imaging. All three centres used the same inclusion and exclusion criteria and the same radiotracer and SPECT/CT imaging protocol. The Swiss study was registered with ClinicalTrials.gov, number NCT00937079.

The study was approved by the local institutional review board of each participating institution, and patients provided written consent in accordance with provisions of the Declaration of Helsinki.

Procedures

Conventional imaging was done by the referring centres, and included triple phase multidetector CT and MRI with 1·5 T or 3·0 T systems and a dedicated circular polarised body array for signal reception. Minimum pulse sequence requirements were multiplanar (axial and coronal) fast spin echo T2-weighted images and axial multiphasic T1-weighted gradient echo images before and after the administration of a gadolinium-containing contrast agent. Additional (optional) pulse sequences included axial gradient dual echo images and axial diffusion weighted images. The appendix summarises CT and MR imaging procedures undertaken at the referral centres.

We did GLP-1R imaging within 2 months of conventional imaging. Synthesis and labelling of ^{111}In-DTPA-exendin-4 has been published elsewhere.[13] We monitored blood sugar concentrations 15 min, 40 min, 60 min, 120 min, 180 min, and 240 min after the injection of ^{111}In-DTPA-exendin-4 and glucose (5%) infusion was administered if needed.

Total-body planar images and single-photon emission CT (SPECT) in combination with CT scans of the abdomen were acquired at 4 h and 3–5 days after injection of 8–14 µg (80–128 MBq) ^{111}In-DTPA-exendin-4. The radiopharmaceutical was intravenously injected over 4–5 min. We did imaging with a combined SPECT/CT unit (Symbia T2 [Siemens Medical Systems, Erlangen, Germany], Infinia Hawkeye [GE Healthcare, Chalfont St Giles, UK], or Bright View XCT [Philips Healthcare, Best, Netherlands]) equipped with a medium-energy, parallel-hole collimator.[18] We used low-dose CT imaging (130 kVp, 40 mAs) to correct for attenuation effects and to provide better anatomical localisation of SPECT findings.

We regarded histological diagnosis as the gold standard for detection of insulinomas. All conventional scans were independently reported by experienced dedicated radiologists at the referral centres. Two experienced nuclear medicine physicians (DW and FF) visually assessed GLP-1R scans. All tissue samples with evidence of adult nesidioblastosis were reviewed by an experienced pathologist (AP). The radiologists, nuclear medicine physicians, and pathologists were masked to the results of other diagnostic tests but were aware of the patients' clinical histories.

Statistical analysis

We regarded positive imaging tests that showed consistency between imaging, surgery, and histological analysis (positive for insulinoma) as true positives. The only exception was made in patients with several lesions. In such patients, the imaging test was regarded as true positive if at least one insulinoma was correctly localised (per patient-based analysis).

For point estimates of sensitivity, specificity, and positive predictive value (PPV), we calculated 95% CI according to the method by Agresti and Coull.[21] For point estimates of the diagnostic odds ratio, we derived 95% CI assuming an approximate normal distribution of the logarithm of the odds ratio.[22]

To compare differences between imaging techniques, on the basis of a small pilot study[18] of six patients we assumed ^{111}In-DTPA-exendin-4 would have a 25% increased detection rate of insulinoma than conventional CT/MRI imaging. With a power of 80% and α of 5%, we planned to enrol 30 patients assuming a dropout rate of 10%.

We assessed significance of the difference in sensitivity and specificity between ^{111}In-DTPA-exendin-4 SPECT/CT and CT/MRI by use of an exact binomial test for dependent proportions as introduced by Mosteller.[23] For comparison of PPVs, we applied the generalised score test.[24] Because estimation of odds ratios was either very imprecise (for the GLP-1R imaging) or not possible (for CT/MRI), we did not consider a comparison of the odds ratios. All analyses were done with R, version 2.15.3.

Role of the funding source

The sponsor of the study had no role in study design, data collection, analysis, interpretation, or writing of the report. The corresponding author, EC, and FF had full access to all the data in this study and had final responsibility for the decision to submit the manuscript.

Results

Between Oct 1, 2008, and Dec 31, 2011, we recruited 30 consecutive patients in neuroendocrine tertiary referral centres (table 1) and referred them to three tertiary nuclear medicine centres. All patients underwent a fasting test. After 4–72 h of fasting, all patients had symptoms of neuroglycopenia (eg, confusion or unconsciousness up to seizure) with low plasma glucose concentrations and inadequately high concentrations of insulin and C-peptide (table 1). 25 (83%) of 30 patients had definite surgical histological diagnosis and were included in the main assessments (figure 1).

CT/MRI assessments were done for 23 (92%) of these 25 patients (figure 1). In two patients, CT and MRI assessments were not done because endoscopic ultrasound was available. Insulinoma was correctly diagnosed by CT/MRI in nine of 19 patients (47% sensitivity, 95% CI 27–68), with a PPV of 100% (95% CI 66–100). Figure 2 shows the contingency table for conventional imaging and histology.

11 (44%) of 25 patients had endoscopic ultrasound, which identified lesions in eight patients. Endoscopic ultrasound localised the insulinoma in seven (88%, 95% CI 66–100) of these patients and islet-cell hyperplasia in the other patient (ie, a false positive). Two patients had a true negative result (islet-cell hyperplasia and no final histological diagnosis) and one patient had a false negative result with endoscopic ultrasound.

Seven (28%) of 25 patients underwent ASVS. The correct vascular territory of the insulinoma was detected in five (71%) of these patients. Two patients with positive results after ASVS did not show any evidence for an insulinoma during or after surgery (false positive). Histological assessment showed islet-cell hyperplasia in one patient and no pathological findings in the other patient.

The labelling yield of ^{111}In-DTPA-exendin-4 was more than 95% with a specific activity of 90 GBq/μmol and a radiochemical purity of 92%. The median decrease in blood glucose level was 1·3 mmol/L (IQR 0·8–2·1; range 0·0–2·6 mmol/L) after injection of ^{111}In-DTPA-exendin-4. The nadir of blood glucose concentrations occurred 40 min after injection. 20 (67%) of 30 patients required an exogenous glucose infusion (5%) for a maximum of 90 min. No serious episodes of hypoglycaemia occurred. The appendix shows a summary of blood glucose findings of each patient before and after injection of ^{111}In-DTPA-exendin-4. We noted no other side-effects.

The longest residence times of ^{111}In-DTPA-exendin-4 were noted in the tumour and kidneys (figure 3), and the clearance of the radiotracer occurred exclusively via the kidneys. For 20 (80%) of 25 patients, GLP-1R imaging

	Participants (n=30)
Age, years	55 (39–75; 25–81)
Sex	
Male	11 (37%)
Female	19 (63%)
Biochemical assessments at the end of the fasting test	
Duration of fasting, h	24 (13–32; 4–72)
Plasma glucose, mmol/L	1·9 (1·7–2·2; 1·0–3·0)
C-peptide, nmol/L	1·11 (0·44–1·90; 0·23–2·50)
Insulin, mU/L	11·0 (6·7–22·0; 1·9–38·0)

Data are median (IQR; range) or n (%).

Table 1: **Baseline characteristics**

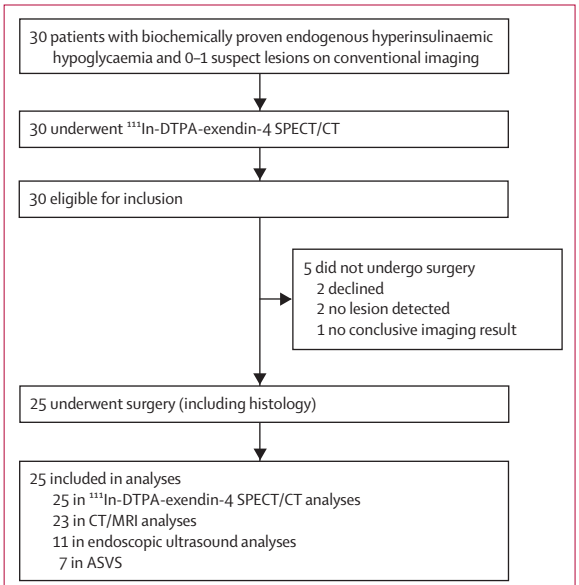

Figure 1: **Study profile**
^{111}In-DTPA-exendin-4=^{111}In-[Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-exendin-4. SPECT/CT=single-photon emission CT in combination with CT. ASVS=selective intra-arterial calcium stimulation and venous sampling.

showed intense focal ^{111}In-DTPA-exendin-4 uptake 4 h after injection. In five patients (patients 14, 19, 25, 26, and 30) only late scans at or after 3 days showed more conclusive results. Histological evaluation in these five patients showed small insulinomas (7–11 mm) in four patients and no conclusive result in one patient.

A 23 patients

CT/MRI		Histology		
		+	–	Total
	+	9	0	9
	–	10	4	14
	Total	19	4	23

B 25 patients

GLP-1R imaging		Histology		
		+	–	Total
	+	19	4	23
	–	1	1	2
	Total	20	5	25

Figure 2: **Contingency tables of conventional imaging and histology (A) and GLP-1R imaging with histology (B)**
GLP-1R=glucagon-like peptide-1 receptor. +=positive. –=negative.

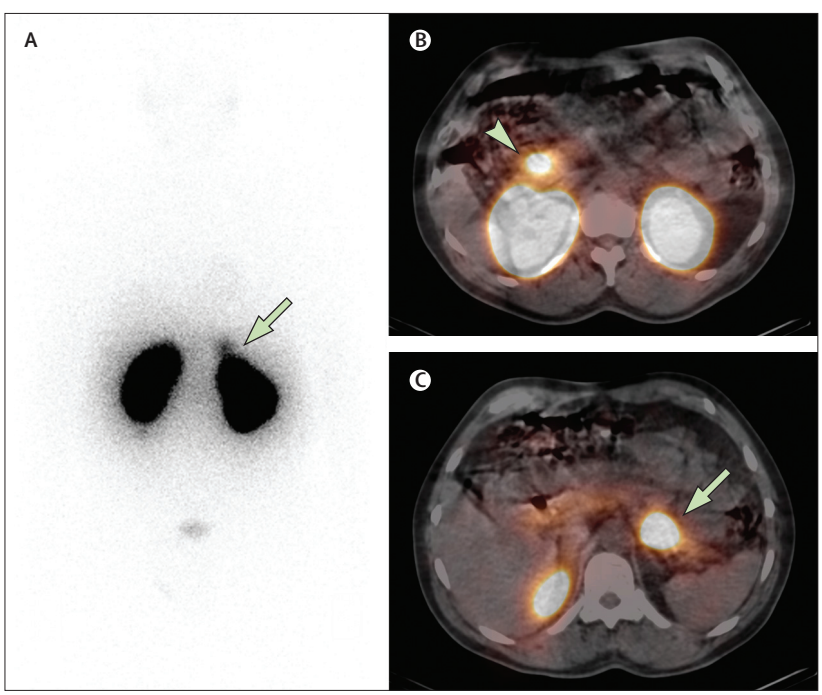

Figure 3: **Whole-body planar image (A) and SPECT/CT images (B and C) from patient 29, 4 h after injection of 108 MBq ^{111}In-DTPA-exendin-4.**
Focal ^{111}In-DTPA-exendin-4 uptake in the head of pancreas (arrowhead) and in the body of the pancreas (arrows). Surgery confirmed an insulinoma in head of pancreas (17 mm) and in the body of pancreas (33 mm). In the tail of pancreas a glucagon-producing neuroendocrine tumour (25 mm) was not detected with GLP-1R imaging. Additional small tumour lesions <10 mm (insulinoma and gastrinomas) were also not detected. ^{111}In-DTPA-exendin-4=^{111}In-[Lys^{40}(Ahx-DTPA-^{111}In)NH$_2$]-exendin-4.

	^{111}In-DTPA-exendin-4 SPECT/CT (n=25)	^{111}In-DTPA-exendin-4 SPECT/CT (n=23*)	CT/MRI (n=23*)	p value*
Sensitivity	95% (75–100)	95% (74–100)	47% (27–68)	0·011
Specificity	20% (2–64)†	25% (3–71)†	100% (45–100)†	1·0†
Positive predictive value	83% (62–94)	86% (65–96)	100% (66–100)	0·069
Diagnostic odds ratio	4·8 (0·24–93)	6·0 (0·29–124)	N/A	N/A

Data are n (95% CI). N/A=not applicable because of missing false-positive results. ^{111}In-DTPA-exendin-4=^{111}In-[Lys^{40}(Ahx-DTPA-^{111}In)NH2]-exendin-4. SPECT/CT=single-photon emission CT in combination with CT. *Based on 23 patients for whom complete imaging was available. †Estimates based on five patients in the ^{111}In-DTPA-exendin-4 SPECT/CT group and four patients in the CT/MRI group.

Table 2: **Comparison of GLP-1R imaging and conventional imaging in patients with suspected insulinoma**

GLP-1R imaging was done in all 25 evaluated patients, showing focal radiotracer uptake in 23 patients (92%). ^{111}In-DTPA-exendin-4 SPECT/CT correctly detected the insulinoma in 19 of 20 patients (95% sensitivity, 95% CI 75–100). The technique had four false positive results (two adult nesidioblastosis and two uncharacterised lesions) resulting in a PPV of 83% (95% CI 62–94; table 2). ^{111}In-DTPA-exendin-4 SPECT/CT was more sensitive than CT/MRI (table 2). Table 2 and figure 2 summarise sensitivity, specificity, PPV, and diagnostic odds ratios for CT/MRI and ^{111}In-DTPA-exendin-4 SPECT/CT.

25 (83%) of 30 patients had a surgical procedure with histological analysis (figure 1, table 3). Surgical planning was based on all available imaging results. All patients had surgery less than 5 weeks after imaging. 20 insulinomas (median size 14 mm [IQR 10–16]) were confirmed histologically, including two patients with multiple endocrine neoplasia type 1 (MEN1) and two patients with malignant insulinoma. Both patients with malignant insulinoma had only one local lymph-node metastasis. In the remaining five patients, changes compatible with adult nesidioblastosis (islet-cell hyperplasia) were diagnosed (three patients), or a definite diagnosis (two patients) could not be established despite use of intraoperative ultrasound, palpation, and biopsy sampling.

Two patients had a confirmed germline mutation of *MEN1*. For both patients, GLP-1R imaging was positive, with one lesion identified in the tail of the pancreas (15 mm) in one patient and two positive lesions identified in the other patient (33 mm and 17 mm; figure 3). Both patients underwent successful operations on the basis of preoperative localisation. Because of the localisation of the two lesions in the second patient, a simultaneous Whipple procedure and a left-sided partial pancreatectomy was done, whereas in the first patient the positive lesion in the tail of the pancreas was removed. Positive lesions noted on GLP-1R imaging in both patients were confirmed as insulinomas on histopathological examination. In addition, histological assessment in the first patient detected two microadenomas of less than 2 mm with insulin staining, which were not detected on GLP-1R imaging or other imaging modalities. In the second patient (patient 29), one further insulin-staining microadenoma (4 mm), one glucagon-staining tumour (25 mm), and two gastrin-staining tumours (9 mm and 6 mm) were identified, which were not identified on GLP-1R imaging or other imaging strategies.

Five patients did not undergo a surgical intervention (figure 1, table 3). Two (patients 18 and 28) had negative conventional imaging and GLP-1R imaging results. Another patient (patient 2) had a negative GLP-1R scan, positive ASVS, and diffusely enhanced uptake in the pancreas with ^{18}F-fluorodopa (^{18}F-DOPA)-PET imaging (data not shown), suggesting islet-cell hyperplasia

	CT/MRI	EUS	ASVS	GLP-1R imaging	Surgery and histology	Final diagnosis	Tumour localisation	Dimension of tumours
Patient 1	TP	Not done	TP	TP	Done	Malignant insulinoma	Uncinate process of pancreas and one local lymph node metastasis	16 mm primary, 15 mm metastasis
Patient 2	–	–	+	–	Not done	No diagnosis	N/A	N/A
Patient 3	TP	Not done	Not done	TP	Done	Benign insulinoma	Head of pancreas	15 mm
Patient 4	TP	TP	Not done	FN	Done	Malignant insulinoma	Tail of pancreas and one local lymph node metastasis	50 mm primary, 11 mm metastasis
Patient 5	TN	Not done	Not done	FP	Done	Histology negative for tumours	N/A	N/A
Patient 6	TN	Not done	Not done	TN	Done	Islet-cell hyperplasia	N/A	N/A
Patient 7	FN	Not done	Not done	TP	Done	Benign insulinoma	Head of pancreas	15 mm
Patient 8	FN	Not done	TP	TP	Done	Benign insulinoma	Head of pancreas	14 mm
Patient 9	Not done	TP	TP	TP	Done	Benign insulinoma	Tail of pancreas	30 mm
Patient 10	TN	FP	FP	FP	Done	Islet-cell hyperplasia	Body and tail of pancreas	N/A
Patient 11	Not done	TN	Not done	FP	Done	Islet-cell hyperplasia	Head of pancreas	N/A
Patient 12	FN	Not done	Not done	TP	Done	Benign insulinoma	Head of pancreas	14 mm
Patient 13	TP	Not done	Not done	TP	Done	Benign insulinoma	Body of pancreas	15 mm
Patient 14	FN	Not done	TP	TP	Done	Benign insulinoma	Head of pancreas	9 mm
Patient 15	–	–	–	+	Not done	No diagnosis, refused surgery	Head of pancreas	N/A
Patient 16	TP	TP	Not done	TP	Done	Multiple insulinomas; MEN1	Tail of pancreas	15 mm (two additional lesions <2 mm were not detected)
Patient 17	FN	Not done	TP	TP	Done	Benign insulinoma	Uncinate process of pancreas	25 mm
Patient 18	–	–	–	–	Not done	No diagnosis	N/A	N/A
Patient 19	TN	TN	FP	FP	Done	Histology negative for tumours	N/A	N/A
Patient 20	+	Not done	Not done	+	Not done	No diagnosis refused surgery	Head of pancreas	N/A
Patient 21	FN	FN	Not done	TP	Done	Benign insulinoma	Body of pancreas	10 mm
Patient 22	FN	TP	Not done	TP	Done	Benign insulinoma	Head of pancreas	14 mm
Patient 23	TP	Not done	Not done	TP	Done	Benign insulinoma	Body of pancreas	15 mm
Patient 24	TP	TP	Not done	TP	Done	Benign insulinoma	Head of pancreas	19 mm
Patient 25	TP	Not done	Not done	TP	Done	Benign insulinoma	Tail of pancreas	11 mm
Patient 26	FN	Not done	Not done	TP	Done	Benign insulinoma	Body tail transition	9 mm
Patient 27	FN	TP	Not done	TP	Done	Benign insulinoma	Head of pancreas	9 mm
Patient 28	Not done	–	–	–	Not done	No diagnosis	N/A	N/A
Patient 29								
Tumour 1	TP	TP	Not done	TP	Done	Multiple insulinomas, MEN1	Head (two lesions) and body of pancreas	17 mm, and 33 mm (one additional lesion of 4 mm was not detected)
Tumour 2	–	–	Not done	–	Done	Multiple gastrinomas, MEN1	Duodenum (two lesions) and one local lymph-node metastasis	6 mm and 9 mm (lymph node metastases not measured)
Tumour 3	–	–	Not done	–	Done	Glucagon-producing neuroendocrine tumour, MEN1	Tail of pancreas	25 mm
Patient 30	FN	Not done	Not done	TP	Done	Benign insulinoma	Body of pancreas	7 mm

EUS=endoscopic ultrasound. ASVS=selective intra-arterial calcium stimulation and venous sampling. GLP-1R=glucagon-like peptide-1 receptor. TP=true positive. –=negative. +=positive. FN=false negative. FP=false positive. TN=true negative. N/A=not applicable. MEN1=multiple endocrine neoplasia type 1.

***Table 3*: Comparison of imaging, surgical, and histological results in 30 patients with suspected insulinoma**

(table 3). Two patients (patients 15 and 20) had a positive GLP-1R scan but declined surgical intervention. All five patients have been treated medically and followed up.

Seven (23%) of 30 patients (patients 7, 12, 21, 26, and 30 with true-positive results and patients 5 and 11 with false-positive results) showed evidence of an insulinoma only on ^{111}In-DTPA-exendin-4 SPECT/CT. For these seven patients, ^{111}In-DTPA-exendin-4 SPECT/CT changed the clinical management by reinforcing the recommendation for surgery. Five of these patients with a proven insulinoma showed a normalisation of blood glucose levels after surgery. In the remaining two patients, only

biopsies of the pancreas were done, which on histology showed islet-cell hyperplasia in one patient and no islet pathology in the second patient.

Discussion

To our knowledge, our prospective multicentre imaging study shows for the first time that GLP-1R imaging is a more sensitive technique than conventional imaging for preoperative localisation of small insulinomas (panel). In our study, seven patients were operated on because GLP-1R imaging was the only method that showed a suspicious lesion in the pancreas. Five of these patients had a confirmed insulinoma with normalisation of hyperinsulinism after surgery, supporting the clinical value of GLP-1R imaging. However, conventional imaging was weakly associated with an increased PPV (100%) compared with GLP-1R imaging (86%; p=0·069). This effect was attributable to an increased rate of false positive results with GLP-1R imaging compared with conventional techniques. Invasive investigations such as endoscopic ultrasound and ASVS also showed false positive results.

Despite our inclusion criteria that required patients to have only one or no suspicious lesion on conventional imaging, two patients had malignant insulinoma, as defined by suspicious lymph nodes identified intraoperatively and confirmed by histological assessment. One patient was positive on GLP-1R imaging and the second patient had a false negative result (the only false negative result on GLP-1R imaging in our study). These findings corroborate a recent report that showed a low detection rate of malignant insulinomas with ^{111}In-DTPA-exendin-4 SPECT/CT.[25] Conventional imaging, by contrast, detected malignant insulinomas in all patients in that study and our own study. Overall, these findings suggest that conventional imaging should be done first to exclude malignant disease whereas GLP-1R imaging could be used after negative conventional imaging.

In a proof-of-principle study,[18] six patients with endogenous hyperinsulinaemic hypoglycaemia were successfully studied with ^{111}In-DOTA-exendin-4. By contrast, our study used DTPA as a chelator, mainly because of the straightforward labelling procedure and high specific activity (90 GBq/µmol for ^{111}In-DTPA-exendin-4 *vs* 20 GBq/µmol for ^{111}In-DOTA-exendin-4), resulting in a smaller peptide load[13,18] and decreasing potential side-effects (eg, nausea, hypoglycaemia). We noted no clinically significant differences in the decrease in glucose concentrations between ^{111}In-DTPA-exendin-4 (median decrease 1·3 mmol/L, IQR 0·8–2·1) and ^{111}In-DOTA-exendin-4 (1·4 mmol/L, IQR 1·1–1·6).[18] In our study, regular monitoring of glucose concentrations after injection led to no serious episodes of hypoglycaemia. Notably, nausea was only reported with the chelator DOTA and not with DTPA. Whether this side-effect is related to the different chelators or to the lower concentration of exendin-4 required when DTPA is used as a chelator has to be proven in future studies. More importantly, different chelators do not seem to affect the sensitivity of GLP-1R imaging.

For four patients, GLP-1R imaging detected false positive lesions. In two of these patients, intraoperative evaluation (palpation, ultrasound, and pancreatic biopsy sampling) did not reveal an insulinoma or islet-cell hyperplasia. The underlying reason for these findings remains unclear. Because one of these lesions was located in the region of the pancreatic head, Brunner's gland of the duodenum (which homogeneously expresses GLP-1R at high density[26]) might have interfered. GLP-1R imaging of islet-cell hyperplasia yielded conflicting findings with two confirmed positive and one negative result. Recently, in-vitro GLP-1R autoradiography of pancreatic tissue of patients with post-bariatric nesidioblastosis[27] showed much the same density of GLP-1R in islet-cell hyperplasia as normal β cells. This

Panel: Research in context

Systematic review

We searched PubMed for studies published in English before Feb 28, 2013, with the terms "insulinoma" and the conventional non-invasive imaging modalities ("computed tomography" and "magnetic resonance imaging"), the invasive modalities ("selective arterial stimulation and venous sampling" and "endoscopic ultrasonography"), and the available methods that use radioisotopes ("Octreoscan", "^{18}F-DOPA-PET", and "GLP-1 receptor imaging"). After exclusion of case reports and narrative reviews, we identified eight relevant prospective studies and 17 relevant retrospective studies. Only three studies reported use of glucagon-like peptide-1 receptors (GLP-1R) imaging in insulinomas, one study was our own proof-of-principle study of six patients, the second study assessed GLP-1R imaging only in malignant insulinoma, and the third study summarised the experience in 11 patients with a different radiotracer to our study (^{99m}Tc-HYNIC-exendin-4). The prospective). The prospective studies included 6–27 patients with endogenous hyperinsulinaemic hypoglycaemia. Sensitivities of CT/MRI for detection of insulinoma ranged from 37% to 59%, selective arterial calcium stimulation and venous sampling (ASVS) from 96% to 100%, and endoscopic ultrasound from 65% to 93%. The sensitivity of GLP-1R imaging was 90% and 100% in the two small studies. The retrospective studies, assessing between six and 237 patients, reported sensitivities of 39–75% with conventional non-invasive imaging, 65–92% for endoscopic ultrasound, and 87–100% for ASVS. The sensitivity of somatostatin receptor 2 imaging using Octreoscan (Covidien, Hazelwood, MO, USA) is usually low (33–50%) and inconsistent for ^{18}F-DOPA-PET (90% in a prospective study and 20% in a retrospective analysis).

Interpretation

Different imaging modalities show a wide range of sensitivity in the detection of insulinomas. Contributors to this difference (beyond the nature of the imaging technology itself) include local availability and competence and experience of the operators. Present data confirm that conventional non-invasive imaging and Octreoscan are less effective than are invasive methods (endoscopic ultrasound and ASVS) for detection of insulinomas. However, this evidence is mainly based on retrospective analysis as few studies have assessed non-invasive techniques with a prospective design. In our prospective study of 30 patients, GLP-1R imaging was superior to conventional imaging in the detection of insulinoma. Furthermore, our data suggest that the sensitivity of GLP-1R imaging is much the same as the performance of the established invasive methods with their inherent risks and costs. Therefore, GLP-1R imaging could become a key component of the preoperative management of patients with endogenous hyperinsulinaemic hypoglycaemia.

finding corresponds to a five-to-six-times lower density of GLP-1R than is noted in insulinomas,[27] thereby potentially explaining the negative GLP-1R scan in the present study. Nesidioblastosis in adults (without previous bariatric surgery) might vary between patients with respect to the number of islets, size of islets, and surface receptors; this variation might explain why GLP-1R imaging of islet-cell hyperplasia could result in positive and negative scans.

Five patients did not undergo a surgical procedure in our study and a final diagnosis could not be established by histology: two had positive GLP-1R scans but declined surgery, two patients had no positive findings on imaging, and one patient had a negative result on GLP-1R imaging, but a positive finding with ASVS and ^{18}F-DOPA PET/CT suggestive of adult nesidioblastosis. Assuming the worst case scenario, all three patients with negative scans might have had a benign insulinoma that was not detectable with the present imaging modalities. Therefore, overestimation of the calculated sensitivity is possible.

Epidemiological data suggest that about 6% of insulinomas are genetically linked to MEN1.[6] In keeping with previous data, two (8%) of our 25 patients who underwent histological assessment had a confirmed germline mutation of *MEN1*.[6] In both patients, GLP-1R imaging was positive with one lesion in one patient and two positive lesions in a second patient. Histological assessment of both patients revealed additional insulin-staining microadenomas not detected by GLP-1R or other imaging with diameters of 2–4 mm. By contrast, insulinomas of 7 mm and more were detected by GLP-1R imaging, suggesting that the minimum size for detection with this technique is about 7 mm. Notably, gastrin-staining and glucagon-staining tumours were not detected by GLP-1R imaging, underscoring the specificity of the method.

This study has limitations. First, because of differences in local availability, preoperative choice of investigations could not be standardised. However, consensus does not exist about use of an established MRI protocol or a preference for use of CT/MRI in the detection of insulinoma.[28,29] Therefore, comparison between GLP-1R imaging and conventional imaging (CT/MRI) seems reasonable. Second, the specificity of GLP-1R imaging was low (20%), because of a small number of true negative results. This feature, in turn, is related to the high sensitivity of the biochemical assessment done before imaging procedures and underscores the fact that careful biochemical assessment is mandatory to benefit from the high sensitivity of GLP-1R imaging and to avoid false positive results. Third, in our study, conventional imaging had a tendency to underperform compared with the published literature.[2,3,29] This discrepancy might be explained by the fact that many of the patients in the study were referred following negative conventional imaging. Finally the study was slightly underpowered because the protocol suggested 30 patients with a dropout of 10% (ie, 27 patients) but only 23 were included in the MRT/CT versus GLP-1R imaging analysis. Nevertheless, the difference between the imaging modalities was significant.

Overall, our study suggests that GLP-1R imaging is a more sensitive method for detection of insulinomas than is CT/MRI and changes clinical management in a substantial percentage of patients with endogenous hyperinsulinaemic hypoglycaemia. Our limited experience with insulinoma in the context of MEN1 suggests that GLP-1R imaging can detect lesions in these patients. The detection of islet-cell hyperplasia by GLP-1R imaging is inconsistent.

Contributors

EC, DW, PJE, JCR, and FF participated in the design and concept of the study. EC, MEC, MBr, TC, SF, CS, JS, and BG recruited patients. DW and MBé prepared the radiotracer. DW, SE, GN, and FF did the imaging and collected data. TC and BG did the surgeries and AP did the pathological review. EC, DW, SE, and FF participated in the data analysis and in the interpretation of results. All authors participated in drafting and finalising the report.

Conflicts of interest

MBé declares that he is an inventor and holder of the following patent: Invention affecting GLP-1 and exendin (Philipps-Universität Marburg, June 17, 2009). All other authors declare that they have no conflicts of interest.

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