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Title.

Utility of ^{68}Ga-DOTA-Exendin-4 PET/CT imaging in distinguishing between insulinoma and nesidioblastosis in patients with confirmed endogenous hyperinsulinaemic hypoglycaemia.

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Abstract;

Background:

Because management is very different, it is important to differentiate between small focal insulinomas and diffuse pancreatic dysplasia (nesidioblastosis) in patients with confirmed

endogenous hyperinsulinaemic hypoglycaemia (EHH). Most insulinomas highly express Glucagon Like Peptide-1 receptors enabling PET/CT imaging with its radiolabelled analogue; ^{68}Ga-DOTA-exendin-4 (Exendin).

Aim:

To determine (a) the utility of Exendin in EHH patients in a clinical setting; (b) whether degree of Exendin uptake differentiates non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) from post gastric bypass hypoglycaemia (PGBH).

Methods

This retrospective study reviewed the clinical, biochemistry and prior imaging findings in confirmed EHH patients referred for Exendin. Accuracy of Exendin was based on surgical findings and treatment outcomes. Finally, average Exendin uptake (SUVmax) of 5 PGBH studies was compared with the SUVmax of a key NIPHS case report [1].

Results:

20/25 consecutive patients had confirmed EHH. Exendin located insulinomas in 8/9 patients enabling successful surgical excision with rapid and durable cure. Exendin correctly identified diffuse nesidioblastosis in 2/3 cases requiring partial pancreatectomy for hypoglycaemia control. All 3 relapsed within 1.7 years with 1 needing completion pancreatectomy. Establishing the cause in the remainder relied on other investigations, clinical correlation and response to empirical treatment. Finally, Exendin SUVmax could not distinguish between NIPHS and PGBH.

Conclusion:

In EHH patients, Exendin accurately identifies the site of insulinoma and thereby differentiates it from nesidioblastosis but negative findings should not be ignored. Exendin is unlikely to differentiate between normal pancreatic uptake, NIPHS and PGBH. **(239 words)**

Introduction.

Benign insulinoma is the commonest cause of adults presenting with biochemical and symptomatic evidence of endogenous hyperinsulinaemic hypoglycaemia (EHH) [2]. Given their small size (usually <2cm) accurate localisation is necessary to reduce morbidity of pancreatic surgery, which is the definitive treatment. Recent prospective multicentre comparison studies demonstrated that conventional imaging has limited sensitivity: CT (65%-70%), MRI (55%-66%) and endoscopic ultrasonography (EUS) (75%-84%} [3, 4].

The current gold standard, selective arterial calcium stimulation and venous sampling studies (CaS), had higher sensitivity (85%) but limited localisation [4-6]. There is potential merit in non-invasive approaches to diagnosis that would replace or complement the need for invasive CaS. Pivotal autoradiographic studies by Reubi *et al.* [7] identified high density glucagon like peptide-1 (GLP-1) receptors and a lower density of somatostatin receptor-2 receptors in >95% and 69% of insulinomas respectively. This led to the development of radiolabelled GLP-1 agents for SPECT/CT and PET/CT imaging that identify the insulinoma site as a focal lesion with greater intensity than in the surrounding pancreas. The most sensitive of these tracers, ^{68}Ga-DOTA-exendin-4 (Exendin), was able to localise > 78% of insulinomas in select patient groups [8-10]. Additionally, insulinomas with a negative Exendin scan may still be located with ^{68}Ga-somatostatin-2 (SSR-2) imaging [2, 11].

Other causes of EHH are classified (Cryer, 2009 #27} as non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), which is the most common subtype of diffuse adult nesidioblastosis representing up to 5% of all EHH cases [12, 13]. A much rarer cause is adult focal nesidioblastosis, which affects only a portion of the pancreatic tissue and, thus, may be amenable to partial pancreatectomy confined to the site of disease [1, 14] First described by Laidlaw in 1938, nesidioblastosis is a functional disorder of pancreatic islet cells characterised by neogenesis of pancreatic ductal epithelium with hypertrophy, hyperplasia and proliferation of beta cells. There is also an increasing incidence of post gastric bypass

hypoglycaemia (PGBH) (13% over 5 years) [12, 15]. Case reports of nesidioblastosis following other upper gastrointestinal surgery such as fundoplication and oesophagectomy are also appearing [16].

There is limited data on the utility of semi quantitative Exendin imaging in a clinical setting where less strict entry criteria are used to investigate these patients. One such prospective clinical study by Sowa-Staszczak *et al.* [17] using a ^{99m}Tc labelled GLP-1 analogue was able to accurately identify insulinomas, but many of the patients remained under observation, were lost to follow-up or had no definite diagnoses.

The aim of the study was to review the clinical use of Exendin imaging at our quaternary molecular imaging referral centre, including accuracy, side-effects, clinical outcomes and interobserver agreement of Exendin imaging in patients with suspected insulinoma. This study also examines whether semi-quantitative Exendin imaging may differentiate adult NIPHS from PGBH as suggested in a case report by Christ et al [1].

Material and Methods

This is a retrospective audit of 24 consecutive patients (25 scans) between July 2014 and September 2019. Patients were referred to undergo Exendin imaging at the Peter MacCallum Cancer Centre (PMCC) to locate or exclude the presence of an insulinoma. The 20 studies with biochemically confirmed EHH are the cohort for the major elements of this study. Data from all 25 studies were only used for interobserver concordance and individual reader's accuracy.

The study protocol and waiver of the requirement for patient consent was approved by the institutional ethics committee(19/181R). The study has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013). Issues re patient anonymity have been addressed.

Relevant biochemical tests, clinical findings, results of other imaging modalities and outcomes were obtained from PMCC medical records and referring physicians.

Exendin synthesis was performed in-house based on the method described by Wild et al [18]. Given its half-life, quality control needed to be performed post injection of the tracer.

After a 4 hour fast, Exendin was administered (mean activity 170 MBq) as a slow IV bolus. Blood glucose was measured throughout the study and 10% IV glucose supplementation was commenced if there was clinical concern of hypoglycaemia risk. Patient weight, Exendin dose and uptake time were recorded. PET/CT imaging was performed on one of 3 GE PET CTs (Disco 690 and two 710's) and Siemens Biograph Truepoint 64/40, which had been calibrated to produce comparable semiquantitative patient weight corrected SUVmax measurements [19]. Images were obtained from skull to pelvis commencing on average 75 minutes post injection (2-4minutes/bed position). Delayed imaging at >2 hrs post injection allowing further renal excretion of Exendin, was performed if no insulinoma was initially identified. The acquired PET data were reconstructed using Time of Flight (TOF), Ordered Subset Expectation Maximisation (OSEM): 2 iterations, 18 subsets, Point Spread Function 5mm FWHM. Low dose CT data (AutomA- 40-100, Kv-130, Slice thickness: 3.75, Pitch-1.375) was used for attenuation correction and anatomical localisation.

The presence and location of any presumptive insulinoma identified by Exendin PET/CT was obtained from the clinical PMCC report.

The data from all 25 studies was used for interobserver reproducibility and accuracy. Two experienced nuclear medicine physicians (blinded to clinical and imaging findings). Each recorded (a) the maximum standardised uptake value (SUVmax) [20], of any Exendin foci suggestive of an insulinoma and (b)their location (uncinate process, body & tail). In patients undergoing surgical treatment, the site of any insulinoma or the presence of nesidioblastosis was obtained from their operative pathology reports. Subsequent diagnosis and clinical outcome of all patients was obtained from medical records and follow-up from referring

doctors. Cohen's Kappa score (https://www.socscistatistics.com.tests) was used to determine the strength of interobserver concordance.

Results:

Patient population:

There were 25 studies performed in 24 patients to determine the presence/location of an insulinoma. The cohort consisted of 11 females and 13 males (1 male had 2 studies). See clinical details in Table 1. Whipple's triad was fulfilled in all patients except for patient 12 who was unable to recognise hypoglycaemic symptoms. 20/24 patients had confirmed EHH.

Exendin administration.

Exendin doses had a mean specific activity of 130 GBq/µmol and a radiochemical purity of >92%. Maximal injected Exendin-4 mass was <30 µg.

The details of Exendin administration are found in Table 1(supplementary). The median administered activity of Exendin was 138 (41-216) MBq. Vomiting and/or nausea was noted in 9/21 studies. Several patients were studied with IV glucose already running prior to Exendin infusion, resulting in skewed baseline and nadir blood glucose levels.

Prior imaging results.

In patients undergoing surgery CT identified 5/9 insulinomas (Table 2a) and was false positive for insulinoma in one nesidioblastosis case (pt 10). SSR-2 imaging had a false-positive site for insulinoma in pt 7. In pt 5 (false-negative Exendin study) a subtle lesion was retrospectively identified on review of an SSR-2 scan performed pre-Exendin, at another institution. The CaS was true-positive in 4 cases including pt 5 (also with a positive EUS), false-negative in pt 8, and false-positive in pt 10. In the non-surgical patients (Table 2b), there was one possible

false-positive CT (pt 14), suggesting the presence of focal nesidioblastosis in the pancreatic tail.

Exendin imaging results and outcomes:

Patient details are found in Table 2and Table 2(supplementary). Exendin successfully localised an insulinoma (including an extra-pancreatic site [21]) in 8/9 patients; see Figure 1 and supplementary Figures 1a and 1b. All subsequently had surgical treatment. An avid focus was identified in the uncinate process of the pancreatic remnant of patient 13 (Table 1b) who refused surgery having undergone 2 prior unsuccessful partial pancreatectomies. In the one false-negative study (Pt 5), histological staining of the tumour demonstrated presence of SSR-2 but not GLP-1 receptors [22]. Diffuse nesidioblastosis was histologically confirmed in 3 patients who subsequently required partial pancreatectomy to control hypoglycaemia. Pt 10's Exendin scan also had an abnormal lesion suggesting an uncinate insulinoma. This was not confirmed surgically.

Using various surgical techniques, all 9 patients with pathologically-confirmed insulinoma had successful resection with rapid, complete and durable resolution of hypoglycaemia. This is in contrast with recurrence of EHH despite surgery in all 3 nesidioblastosis patients. Pt 11 (Figure 2) required completion pancreatectomy resulting in development of Type 1 diabetes.

The outcomes of patients not undergoing surgery are outlined in Table 2b. Of interest, 4 had diffuse medically controlled nesidioblastosis, one had autoimmune hypoglycaemia. Patient 20 stopped her diazoxide and remained asymptomatic on no treatment.

Can SUVmax distinguish between NIPHS and PGBH cases?

Table 3 summarises the findings of pancreatic SUVmax obtained from 4 assessable EHH patients (5 scans) with PGBH. The mean SUVmax for readers 1 and 2 were 7.0 and 7.3 respectively. This is essentially the same as the SUVmax (6.9) seen in the NIPHS case

of Christ *et al.* [1]. Unfortunately, accurate SUVmax measurement in the sole proven case of familial NIPHS (pt 12) was not technically feasible due to significant obesity.

Interobserver comparison

Details are found in Table 3 (Supplementary). Inter-reader concordance for all cases was 21/25: (84%) giving a Cohen's Kappa score of: 0.68; which is consistent with substantial agreement. Accuracy was (92%) for reader 1 and 84% for reader 2.

Discussion

This retrospective study confirms that in a clinical setting, Exendin PET/CT imaging is a sensitive and specific non-invasive method of insulinoma localisation. Interobserver reproducibility and specificity was found to be acceptable [2, 11]. Our study also had one confirmed and one biochemically compatible case of diffuse nesidioblastosis following fundoplication; a rare occurrence in adults [16, 23]. The apparent remission seen in pt 21 suggests a cause related to her chronic renal failure rather than NIPHS [24].

Known limitations of Exendin were also observed. False-positives are rare [3] but possible. The single false-negative case in this study was due to lack of GLP-1 receptor expression within the insulinoma. In this situation, an insulinoma usually but not always expresses SSR-2 receptors [2, 11]. In our case, there was just sufficient SSR-2 receptor density to allow it to be identified on a post-surgical review of the outside SSR-2 scan. This insulinoma was pre-operatively located on EUS and CaS. Intense physiologic renal uptake, which can result in reconstruction artefact, may mask Exendin uptake in an adjacent insulinoma within the pancreatic tail. The subtle lesion in pt 8 adjacent to the left kidney [11] was identified by the clinical reader and 1 of the 2 blinded readers. Awareness of this pitfall, newer PET reconstruction algorithms which minimise artefact, 2 hour delayed imaging to allow some renal washout, respiratory gating and more prolonged imaging of the pancreatic region may be needed to make the lesion more obvious. Pharmacological inhibition of renal uptake of

Exendin with succinylated gelatin [25] or brush border membrane degradation [26] is another potential solution. Given the high renal uptake, the kidneys are the radiation dose limiting organs. Consequently, unlike the SSR-2 agents, this tracer may remain unsuitable as a theranostic agent.

There remains uncertainty whether NIPHS may be identifiable with in-vivo Exendin imaging [2]. In vitro studies [27] have already shown that PGBH patients have normal pancreatic GLP-1 receptor density so should not be detectable by Exendin imaging. More recently, Christ *et al.* [1], published a case report showing in-vitro GLP-1 receptor density within the surgical specimen of a patient with excised focal NIPHS, was 3 times normal. This suggested that NIPHS may be identifiable by in-vivo Exendin imaging. The pancreatic SUVmax in this case was 6.9: a finding well within the mean values (7.3 and 7.0) seen in our GPBH patients. Thus, the degree of pancreatic Exendin uptake (SUVmax) may not distinguish normals and Nesidioblastosis associated with NIPHS or PGBH. This is very likely due to major differences between the in-vivo and in-vitro tests.

The limitations of surgical treatment for medically uncontrollable adult nesidioblastosis [28, 29] are illustrated in this series. All three cases underwent relatively conservative surgery and relapsed to a varying degree with one requiring completion pancreatectomy and the other two being partially controlled with medications. This confirms that in such cases, at least subtotal pancreatectomy needs consideration to minimise relapse [28].

The lack of complete information and difficulties with follow up in this series, are some inherent limitations of a retrospective study. Because of minimal FDG uptake into adipose tissue SUVmax with weight correction overestimates real SUVmax by up to 70% in obese patients, [30, 31]. Ga-68 Exendin shares this property, but, the resultant degree of overestimation is not available. Not all patients were fully screened prior to having their Exendin scan. However, in a real-world clinical setting, ill and/or frail patients with multiple co-morbidities or conflicting biochemistry findings, may still need an Exendin study to exclude

the unlikely presence of an insulinoma. Finally, there appears to be no established normal range of pancreatic Exendin SUVmax.

The very high frequency of symptoms related to hypoglycaemia, nausea and vomiting following slow intravenous injection of Exendin is well documented [2]. Thus, it is important to have anti-emetic medication available, closely observe the patient and frequently measure blood glucose from before Exendin administration until the patient leaves the PET/CT suite. This is particularly important during the uptake phase. Our unit now co-administers I.V. glucose commencing prior to injection of Exendin. Syringes containing 50% glucose need to be available until blood sugar levels are in the normal range.

So, what is the role of Exendin in suspected EHH? The first step remains taking a clinical history and full biochemical characterisation. This includes formal demonstration of EHH, and an abnormal 72 hour fasting study to identify the potential presence of an insulinoma. Insulin antibodies are also needed to exclude autoimmune cases of EHH.

Despite the superior accuracy of Exendin imaging in localising insulinomas, it should only be considered when conventional structural imaging is negative. If Exendin imaging suggests the presence of an insulinoma, endoscopic ultrasound may be used to confirm the location. CaS is an important alternative to confirm the presence of an insulinoma or, if uniform pancreatic Exendin uptake is seen, suggesting the presence of nesidioblastosis [5, 6]. If Exendin scan does not demonstrate an insulinoma, additional SSR-2 and/or ^{18}FDG imaging should also be considered.

If structural imaging is positive, the first radionuclide test should be an SSR-2 scan. It is widely available, has a reasonable sensitivity (~70%) for insulinoma identifying a cohort that overlaps with Exendin and is more likely to be positive in the setting of more aggressive tumours including those with metastatic disease. Furthermore, when labelled with a beta emitter (^{177}Lu Dotatate), it can be used as a therapeutic agent [2, 11].

CONCLUSION

This study confirms the substantial clinical benefit of Exendin in distinguishing between insulinomas and nesidioblastosis in patients with biochemically confirmed EHH. Although a combination of SSR-2 and Exendin improves sensitivity, it may still be insufficient to rule out the presence of an insulinoma. Thus, there remains a continuing important back-up role for arterial calcium stimulation venous sampling studies. Semiquantitative analysis of pancreatic Exendin uptake (SUVmax) may not distinguish between normal, diffuse NIPHS and PGBH patients.

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Figure legends:

Figure: 1 The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 3 show the site of a pancreatic uncinate insulinoma only on the PET component. However it was identified on an outside contrast CT.

Figure: 1a (Supplementary). The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 4 show the site of a pancreatic body insulinoma only on the PET component. However, it was identified on an outside Contrast CT.

Figure: 1b (Supplementary). The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 6 show the site of a pancreatic tail insulinoma only on the PET component. This patient had a negative outside contrast CT study.

Figure 2: The transaxial co-registered (PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) in patient 11 with proven nesidioblastosis, show relatively uniform Exendin uptake throughout the pancreas, a normal coregistered CT and a normal outside contrast CT. The pancreatic SUVmax measured in this case was 10.

Table 1: Clinical details of 20 EHH patient scans

pt no	age (yrs)	relevant history	symptom description & duration	(yrs)	Fasting	PPH
1	14		Seizures in morning	0.5		
2	30		Sweats, slurred speech	7		
3	66		Headache, blurred vision	1.5		
4	66		Collapsed: hypoglycaemia	0.2	+ve	
5	82	NIDDM diet	Confusion, vision loss	3	+ve	
6	33		Confusion, anxiety	0.5		
7	50		Collapse: Unaware hypo	0.2		
8	58		Confusion, sweats,	1.6	+ve	
9	64	Prior NIDDM	Tremors, sweats, drowsy	1	+ve	
10	66	Fundoplication 1991, 2015	Blurred vision, sweats	3	-ve	+ve
11	37	Bariatric surgery 2014	Blackouts	2		+ve
12	23	Obesity, mother had NIPHS as 6y/0	Sweats, hunger, unaware	0.3	+ve	
13	60	Occult insulinoma, post-surgery	Seizures, confusion	28		
14	60	fundoplication, alcohol, Sarcoid	Tremor, sweats, collapse	l0.5	-ve	
15	74	Prior NIDDM,	Dementia ? symptoms			
18	69	CVD	Confusion/collapse	1		+ve
19	52	Bariatric surgery '95,'00,'12	Dizziness, sweats	6	-ve	+ve
20	26	Epilepsy (on Epilim)	Neuroglycopenic	0.8	-ve	
21	71	CVD, CRF, Cushing's, NIDDM	Unstable angina, drowsy	0.5		
24	37	8 Co-morbidities, hypoglycaemia	Syncope, sweating	2	-ve	+ve
10	67	Relapse post-surgery	Blurred vision, sweats	0.6		

NIDDM. non-insulin dependent diabetes mellitus, CVD: Cardiovascular disease, +ve: positive
Fast: 72 hr fasting study, -ve: negative, +/-: equivocal, PPH: post prandial hypoglycaemia
CRF: chronic renal failure, EHH: endogenous hyperinsulinaemic hypoglycaemia

Table 2: Imaging, treatment and outcomes in patients with EHH

Pt No	Other tests	GLP-1 lesion Location	Final Diagnosis	treatment & status at April 2020	
A) Patients treated surgically					
1	CT+/-	Body/tail	Insulinoma	Enucleation	Cured
2	CaS+ CT+	Body/tail	Insulinoma	Distal	Cured
3	CT+ SSR-	Uncinate	Insulinoma	Duod	Cured
4	CT+ SSR-	Body	Insulinoma	Duod	Cured
5	CaS+ CT- EUS+ SSR+ ^	Nil*	Insulinoma	Laparoscopic	Cured
6	**CaS+ CT- IOUS+**	Uncinate	Insulinoma	Distal	Cured
7	CT+ MRI+ SSR+(tail)**	Uncinate	Insulinoma	Duod	Cured
8	CaS- CT- MRI- EUS+	Tail	Insulinoma	Distal	Cured
9	CT & MRI: splenunculus	Extra pancr	Insulinoma	Laparoscopic	Cured
10	CaS+** CT+ **	Uncinate**	PGBH	Duod #50%	Recurred: 0.7 yrs
11	CT- MRI-	Diffuse	PGBH	Distal #67%	Recurred: 0.5 yrs
12	CaS+ Tail CT- EUS-	Diffuse	NIPHS	Distal	Recurred :1.5 yrs
B) Non-operative patients					
13	CT- EUS- SSR- US-	Uncinate	Insulinoma	Refused surgery, well on diazoxide	
14	CT+,(tail) FDG- SSR-	Diffuse	PGBH	Stable on diazoxide, off alcohol	
15	CT- EUS-	Diffuse	Unknown	Lost to follow-up soon after scan	
18	CT- SSR- Ins ab: +ve	Diffuse	Autoimmune	Cured on stopping clopidogrel	
19	CT- SSR-	Diffuse	PGBH	Creon and jejunal feeds	
20	CT- EUS-	Diffuse	MDM: Nesid	Well controlled on diazoxide	
21	CT- MRI- SSR-	Diffuse	CRF,	Still well after stopping diazoxide	
24	CT- EUS- FDG- SSR-	Diffuse	?NIPHS	Therapy: no better, refused surgery	
10	CT- MRI- SSR-	Diffuse	PGBH	Better on diazoxide & jejunostomy	

pancr: pancreatic, Duod: duodenopancreatectomy, Distal: distal pancreatectomy, EUS: endoscopic ultrasound , CaS: calcium stimulation, IOUS: intraoperative US, *: false negative, **: false positive, ^: positive on retrospective review, MDM: multidisciplinary meeting, Nesid: nesidioblastosis, #: extent of pancreatic resection, Insab: insulin antibodies. , CRF: chronic renal failure.

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Table 3 Pancreatic Exendin SUVmax in PGBH pts

pt no	relevant clinical details	72 hr Fast	Reader 1 SUVmax	Reader 2 SUVmax
10	Fundoplication 1991, 2015	-ve	5	4.9
11	bariatric surgery		9.8	10
14	fundoplication, alcohol, Sarcoid	-ve	8.7	8.7
19	gastric bypasses x3, jejunostomy	-ve	6.2	5
10	relapse post-surgery		6.8	6.2
	SUVmax:	mean	7.3	7.0
		S.D.	1.9	2.3

Table 1 (supplementary) Exendin scan details

Pt no	Weight (Kg)	Ga68 dose (MBq)	Uptake (min)	Exendin symptoms	Glucose baseline	(mM/L) nadir	Glucose given
1	59	138	81	N&V	5.9	3.4	IVR
2	107	105	79	N	4.9	2.8	IV
3	79	87	62		7.9	5.2	IVR
4	102	216	60		3.7	3.7	IVR
5	52	128	81		4.4	2.6	O & IV
6	68	41	51		5.3	2.6	IVR
7	138	88	85		2.9	2.9	IVR
8	69	148	74	N&V	5.2	3.4	oral
9	131	288	118	N&V	5.8	3.9	oral
10	77	145	81	N	8.1	4.1	IV R
11	68	70	78	N	5.5	3.8	O & IV
12	151	140	85		4.7	2.7	IVR
13	92	87	67		4.1	2.1	IV
14	91	226	60		7.1	2.7	O & IV
15	38	96	76		5	3.5	IV
18	66	207	95		3.4	3.2	IVR
19	56	68	75	N	2.9	4.9	No
20	77	174	62	N&V	6.6	3.4	IV
21	71	111	60		3.8	2.9	IV
24	63	180	85		4.8	4.3	IV
10	77	145	81	N&V	7.8	5.1	IVR

N: nausea; V: vomiting, IV: Intra-venous glucose during Exendin uptake.
IVR: IV glucose running before Exendin was given.

Table 2 (supplementary) : Details of surgical findings

Pt No	GLP-1 diagnosis	GLP-1 lesion location	Tumour site at surgery	Tumour size (mm)	Tumour K-67
1	Insulinoma	Body/tail	Same	12	<1%
2	Insulinoma	Body/tail	Same	13x3x15	<2%
3	Insulinoma	Uncinate	Same	18x15x15	1%
4	Insulinoma	Body	Same	21	1%
5	Diffuse*	Nil*	Tail	11x6	
6	Insulinoma	Tail	Same	9x7	<1%
7	Insulinoma	Uncinate	Same	21	<2%
8	Insulinoma	Tail	Same	13x14	
9	Insulinoma	Extra pancreatic	Same	15x10x10	<1%
10	Insulinoma**	Uncinate**	Same		
11	Diffuse	Diffuse	Nesid		
12	Diffuse	Diffuse	Nesid		

*: false negative, **: false positive; Nesid: nesidioblastosis.

Table3 (supplementary) : Reader concordance and accuracy

Pt	Reader 1:		Reader 2:		Readers	Cohen's Kappa		
						Reader		Only
no	SUVmax lesion	Correct	SUVmax lesion	Correct	Agree	Agreement +ve	-ve	Reader 2 +ve
1	10.6	1	10.6	1	1	1		
2	23.6	1	24.0	1	1	1		
3	12.4	1	12.4	1	1	1		
4	24.3	1	24.0	1	1	1		
5					1	1		
6	14.0	1	14.0	1	1	1		
7	17.0	1	17.0	1	1	1		
8			6.7					1
9	24.3	1	24.0	1	1	1		
10		1	7.3	1				1
11		1		1	1		1	
12		1		1	1		1	
13	14.0	1	14.0	1	1	1		
14		1	8.7					1
15		1		1	1		1	
16		1		1	1		1	
17		1		1	1		1	
18		1		1	1		1	
19		1		1	1		1	
20		1	6.9					1
21		1		1	1		1	
22		1		1	1		1	
23		1		1	1		1	
24		1		1	1		1	
10		1		1	1		1	
Total correct		23		21	21	8	13	4

Reader agreement= 83%, Cohens Kappa= 0.65 ie suggests substantial agreement.
Lesion: SUVmax of potential insulinoma

Abstract;

Background:

Because management is very different, it is important to differentiate between small focal insulinomas and diffuse pancreatic dysplasia (nesidioblastosis) in patients with confirmed endogenous hyperinsulinaemic hypoglycaemia (EHH). Most insulinomas highly express Glucagon Like Peptide-1 receptors enabling PET/CT imaging with its radiolabelled analogue; ^{68}Ga-DOTA-exendin-4 (Exendin).

Aim:

To determine (a) the utility of Exendin in EHH patients in a clinical setting; (b) whether degree of Exendin uptake differentiates non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS) from post gastric bypass hypoglycaemia (PGBH).

Methods

This retrospective study reviewed the clinical, biochemistry and prior imaging findings in confirmed EHH patients referred for Exendin. Accuracy of Exendin was based on surgical findings and treatment outcomes. Finally, average Exendin uptake (SUVmax) of 5 PGBH studies was compared with the SUVmax of a key NIPHS case report [1].

Results:

20/25 consecutive patients had confirmed EHH. Exendin located insulinomas in 8/9 patients enabling successful surgical excision with rapid and durable cure. Exendin correctly identified diffuse nesidioblastosis in 2/3 cases requiring partial pancreatectomy for hypoglycaemia control. All 3 relapsed within 1.7 years with 1 needing completion pancreatectomy. Establishing the cause in the remainder relied on other investigations, clinical correlation and response to empirical treatment. Finally, Exendin SUVmax could not distinguish between NIPHS and PGBH.

Conclusion:

In EHH patients, Exendin accurately identifies the site of insulinoma and thereby differentiates it from nesidioblastosis but negative findings should not be ignored. Exendin is unlikely to differentiate between normal pancreatic uptake, NIPHS and PGBH. **(239 words)**

MAIN TEXT File

Introduction.

Benign insulinoma is the commonest cause of adults presenting with biochemical and symptomatic evidence of endogenous hyperinsulinaemic hypoglycaemia (EHH) [2]. Given their small size (usually <2cm) accurate localisation is necessary to reduce morbidity of pancreatic surgery, which is the definitive treatment. Recent prospective multicentre comparison studies demonstrated that conventional imaging has limited sensitivity: CT (65%-70%), MRI (55%-66%) and endoscopic ultrasonography (EUS) (75%-84%} [3, 4].

The current gold standard, selective arterial calcium stimulation and venous sampling studies (CaS), had higher sensitivity (85%) but limited localisation [4-6]. There is potential merit in non-invasive approaches to diagnosis that would replace or complement the need for invasive CaS. Pivotal autoradiographic studies by Reubi *et al.* [7] identified high density glucagon like peptide-1 (GLP-1) receptors and a lower density of somatostatin receptor-2 receptors in >95% and 69% of insulinomas respectively. This led to the development of radiolabelled GLP-1 agents for SPECT/CT and PET/CT imaging that identify the insulinoma site as a focal lesion with greater intensity than in the surrounding pancreas. The most sensitive of these tracers, ^{68}Ga-DOTA-exendin-4 (Exendin), was able to localise > 78% of insulinomas in select patient groups [8-10]. Additionally, insulinomas with a negative Exendin scan may still be located with ^{68}Ga-somatostatin-2 (SSR-2) imaging [2, 11].

Other causes of EHH are classified (Cryer, 2009 #27} as non-insulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), which is the most common subtype of diffuse adult nesidioblastosis representing up to 5% of all EHH cases [12, 13]. A much rarer cause is adult focal nesidioblastosis, which affects only a portion of the pancreatic tissue and, thus, may be amenable to partial pancreatectomy confined to the site of disease [1, 14] First described by Laidlaw in 1938, nesidioblastosis is a functional disorder of pancreatic islet cells characterised by neogenesis of pancreatic ductal epithelium with hypertrophy, hyperplasia and proliferation of beta cells. There is also an increasing incidence of post gastric bypass hypoglycaemia (PGBH) (13% over 5 years) [12, 15]. Case reports of nesidioblastosis following other upper gastrointestinal surgery such as fundoplication and oesophagectomy are also appearing [16].

There is limited data on the utility of semi quantitative Exendin imaging in a clinical setting where less strict entry criteria are used to investigate these patients. One such prospective clinical study by Sowa-Staszczak *et al.* [17] using a ^{99m}Tc labelled GLP-1 analogue was able to accurately identify insulinomas, but many of the patients remained under observation, were lost to follow-up or had no definite diagnoses.

The aim of the study was to review the clinical use of Exendin imaging at our quaternary molecular imaging referral centre, including accuracy, side-effects, clinical outcomes and interobserver agreement of Exendin imaging in patients with suspected insulinoma. This study also examines whether semi-quantitative Exendin imaging may differentiate adult NIPHS from PGBH as suggested in a case report by Christ et al [1].

Material and Methods

This is a retrospective audit of 24 consecutive patients (25 scans) between July 2014 and September 2019. Patients were referred to undergo Exendin imaging at the Peter MacCallum Cancer Centre (PMCC) to locate or exclude the presence of an insulinoma. The 20 studies with biochemically confirmed EHH are the cohort for the major elements of this study. Data from all 25 studies were only used for interobserver concordance and individual reader's accuracy.

The study protocol and waiver of the requirement for patient consent was approved by the institutional ethics committee(19/181R). The study has been performed in accordance with the ethical standards laid down in an appropriate version of the Declaration of Helsinki (as revised in Brazil 2013). Issues re patient anonymity have been addressed.

Relevant biochemical tests, clinical findings, results of other imaging modalities and outcomes were obtained from PMCC medical records and referring physicians.

Exendin synthesis was performed in-house based on the method described by Wild et al [18]. Given its half-life, quality control needed to be performed post injection of the tracer.

After a 4 hour fast, Exendin was administered (mean activity 170 MBq) as a slow IV bolus. Blood glucose was measured throughout the study and 10% IV glucose supplementation was commenced if there was clinical concern of hypoglycaemia risk. Patient weight, Exendin dose and uptake time were recorded. PET/CT imaging was performed on one of 3 GE PET CTs (Disco 690 and two 710's) and Siemens Biograph Truepoint

64/40, which had been calibrated to produce comparable semiquantitative patient weight corrected SUVmax measurements [19]. Images were obtained from skull to pelvis commencing on average 75 minutes post injection (2-4minutes/bed position). Delayed imaging at >2 hrs post injection allowing further renal excretion of Exendin, was performed if no insulinoma was initially identified. The acquired PET data were reconstructed using Time of Flight (TOF), Ordered Subset Expectation Maximisation (OSEM): 2 iterations, 18 subsets, Point Spread Function 5mm FWHM. Low dose CT data (AutomA- 40-100, Kv-130, Slice thickness: 3.75, Pitch-1.375) was used for attenuation correction and anatomical localisation.

The presence and location of any presumptive insulinoma identified by Exendin PET/CT was obtained from the clinical PMCC report.

The data from all 25 studies was used for interobserver reproducibility and accuracy. Two experienced nuclear medicine physicians (blinded to clinical and imaging findings). Each recorded (a) the maximum standardised uptake value (SUVmax) [20], of any Exendin foci suggestive of an insulinoma and (b)their location (uncinate process, body & tail). In patients undergoing surgical treatment, the site of any insulinoma or the presence of nesidioblastosis was obtained from their operative pathology reports. Subsequent diagnosis and clinical outcome of all patients was obtained from medical records and follow-up from referring doctors. Cohen's Kappa score (https://www.socscistatistics.com.tests) was used to determine the strength of interobserver concordance.

Results:

Patient population:

There were 25 studies performed in 24 patients to determine the presence/location of an insulinoma. The cohort consisted of 11 females and 13 males (1 male had 2 studies). See clinical details in Table 1. Whipple's triad was fulfilled in all patients except for patient 12 who was unable to recognise hypoglycaemic symptoms. 20/24 patients had confirmed EHH.

Exendin administration.

Exendin doses had a mean specific activity of 130 GBq/µmol and a radiochemical purity of >92%. Maximal injected Exendin-4 mass was <30 µg.

The details of Exendin administration are found in Table 1(supplementary). The median administered activity of Exendin was 138 (41-216) MBq. Vomiting and/or nausea was noted in 9/21 studies. Several patients were studied with IV glucose already running prior to Exendin infusion, resulting in skewed baseline and nadir blood glucose levels.

Prior imaging results.

In patients undergoing surgery CT identified 5/9 insulinomas (Table 2a) and was false positive for insulinoma in one nesidioblastosis case (pt 10). SSR-2 imaging had a false-positive site for insulinoma in pt 7. In pt 5 (false-negative Exendin study) a subtle lesion was retrospectively identified on review of an SSR-2 scan performed pre-Exendin, at another institution. The CaS was true-positive in 4 cases including pt 5 (also with a positive EUS), false-negative in pt 8, and false-positive in pt 10. In the non-surgical patients (Table 2b), there was one possible false-positive CT (pt 14), suggesting the presence of focal nesidioblastosis in the pancreatic tail.

Exendin imaging results and outcomes:

Patient details are found in Table 2and Table 2(supplementary). Exendin successfully localised an insulinoma (including an extra-pancreatic site [21]) in 8/9 patients; see Figure 1 and supplementary Figures 1a and 1b. All subsequently had surgical treatment. An avid focus was identified in the uncinate process of the pancreatic remnant of patient 13 (Table 1b) who refused surgery having undergone 2 prior unsuccessful partial pancreatectomies. In the one false-negative study (Pt 5), histological staining of the tumour demonstrated presence of SSR-2 but not GLP-1 receptors [22]. Diffuse nesidioblastosis was histologically confirmed in 3 patients who subsequently required partial pancreatectomy to control hypoglycaemia. Pt 10's Exendin scan also had an abnormal lesion suggesting an uncinate insulinoma. This was not confirmed surgically.

Using various surgical techniques, all 9 patients with pathologically-confirmed insulinoma had successful resection with rapid, complete and durable resolution of hypoglycaemia. This is in contrast with recurrence of EHH despite surgery in all 3 nesidioblastosis patients. Pt 11 (Figure 2) required completion pancreatectomy resulting in development of Type 1 diabetes.

The outcomes of patients not undergoing surgery are outlined in Table 2b. Of interest, 4 had diffuse medically controlled nesidioblastosis, one had autoimmune hypoglycaemia. Patient 20 stopped her diazoxide and remained asymptomatic on no treatment.

Can SUVmax distinguish between NIPHS and PGBH cases?

Table 3 summarises the findings of pancreatic SUVmax obtained from 4 assessable EHH patients (5 scans) with PGBH. The mean SUVmax for readers 1 and 2 were 7.0 and 7.3 respectively. This is essentially the same as the SUVmax (6.9) seen in the NIPHS case of Christ *et al.* [1]. Unfortunately, accurate SUVmax measurement in the sole proven case of familial NIPHS (pt 12) was not technically feasible due to significant obesity.

Interobserver comparison

Details are found in Table 3 (Supplementary). Inter-reader concordance for all cases was 21/25: (84%) giving a Cohen's Kappa score of: 0.68; which is consistent with substantial agreement. Accuracy was (92%) for reader 1 and 84% for reader 2.

Discussion

This retrospective study confirms that in a clinical setting, Exendin PET/CT imaging is a sensitive and specific non-invasive method of insulinoma localisation. Interobserver reproducibility and specificity was found to be acceptable [2, 11]. Our study also had one confirmed and one biochemically compatible case of diffuse nesidioblastosis following fundoplication; a rare occurrence in adults [16, 23]. The apparent remission seen in pt 21 suggests a cause related to her chronic renal failure rather than NIPHS [24].

Known limitations of Exendin were also observed. False-positives are rare [3] but possible. The single false-negative case in this study was due to lack of GLP-1 receptor expression within the insulinoma. In this situation, an insulinoma usually but not always expresses SSR-2 receptors [2, 11]. In our case, there was just sufficient SSR-2 receptor density to allow it to be identified on a post-surgical review of the outside SSR-2 scan. This insulinoma was pre-operatively located on EUS and CaS. Intense physiologic renal uptake, which can result in reconstruction artefact, may mask Exendin uptake in an adjacent insulinoma within the pancreatic tail. The subtle lesion in pt 8 adjacent to the left kidney [11] was identified by the clinical reader and

1 of the 2 blinded readers. Awareness of this pitfall, newer PET reconstruction algorithms which minimise artefact, 2 hour delayed imaging to allow some renal washout, respiratory gating and more prolonged imaging of the pancreatic region may be needed to make the lesion more obvious. Pharmacological inhibition of renal uptake of Exendin with succinylated gelatin [25] or brush border membrane degradation [26] is another potential solution. Given the high renal uptake, the kidneys are the radiation dose limiting organs. Consequently, unlike the SSR-2 agents, this tracer may remain unsuitable as a theranostic agent.

There remains uncertainty whether NIPHS may be identifiable with in-vivo Exendin imaging [2]. In vitro studies [27] have already shown that PGBH patients have normal pancreatic GLP-1 receptor density so should not be detectable by Exendin imaging. More recently, Christ *et al.* [1], published a case report showing in-vitro GLP-1 receptor density within the surgical specimen of a patient with excised focal NIPHS, was 3 times normal. This suggested that NIPHS may be identifiable by in-vivo Exendin imaging. The pancreatic SUVmax in this case was 6.9: a finding well within the mean values (7.3 and 7.0) seen in our GPBH patients. Thus, the degree of pancreatic Exendin uptake (SUVmax) may not distinguish normals and Nesidioblastosis associated with NIPHS or PGBH. This is very likely due to major differences between the in-vivo and in-vitro tests.

The limitations of surgical treatment for medically uncontrollable adult nesidioblastosis [28, 29] are illustrated in this series. All three cases underwent relatively conservative surgery and relapsed to a varying degree with one requiring completion pancreatectomy and the other two being partially controlled with medications. This confirms that in such cases, at least subtotal pancreatectomy needs consideration to minimise relapse [28].

The lack of complete information and difficulties with follow up in this series, are some inherent limitations of a retrospective study. Because of minimal FDG uptake into adipose tissue SUVmax with weight correction overestimates real SUVmax by up to 70% in obese patients, [30, 31]. Ga-68 Exendin shares this property, but, the resultant degree of overestimation is not available. Not all patients were fully screened prior to having their Exendin scan. However, in a real-world clinical setting, ill and/or frail patients with multiple co-morbidities or conflicting biochemistry findings, may still need an Exendin study to exclude the unlikely presence of an insulinoma. Finally, there appears to be no established normal range of pancreatic Exendin SUVmax.

The very high frequency of symptoms related to hypoglycaemia, nausea and vomiting following slow intravenous injection of Exendin is well documented [2]. Thus, it is important to have anti-emetic medication available, closely observe the patient and frequently measure blood glucose from before Exendin administration until the patient leaves the PET/CT suite. This is particularly important during the uptake phase. Our unit now co-administers I.V. glucose commencing prior to injection of Exendin. Syringes containing 50% glucose need to be available until blood sugar levels are in the normal range.

So, what is the role of Exendin in suspected EHH? The first step remains taking a clinical history and full biochemical characterisation. This includes formal demonstration of EHH, and an abnormal 72 hour fasting study to identify the potential presence of an insulinoma. Insulin antibodies are also needed to exclude autoimmune cases of EHH.

Despite the superior accuracy of Exendin imaging in localising insulinomas, it should only be considered when conventional structural imaging is negative. If Exendin imaging suggests the presence of an insulinoma, endoscopic ultrasound may be used to confirm the location. CaS is an important alternative to confirm the presence of an insulinoma or, if uniform pancreatic Exendin uptake is seen, suggesting the presence of nesidioblastosis [5, 6]. If Exendin scan does not demonstrate an insulinoma, additional SSR-2 and/or ^{18}FDG imaging should also be considered.

If structural imaging is positive, the first radionuclide test should be an SSR-2 scan. It is widely available, has a reasonable sensitivity (~70%) for insulinoma identifying a cohort that overlaps with Exendin and is more likely to be positive in the setting of more aggressive tumours including those with metastatic disease. Furthermore, when labelled with a beta emitter (^{177}Lu Dotatate), it can be used as a therapeutic agent [2, 11].

CONCLUSION

This study confirms the substantial clinical benefit of Exendin in distinguishing between insulinomas and nesidioblastosis in patients with biochemically confirmed EHH. Although a combination of SSR-2 and Exendin improves sensitivity, it may still be insufficient to rule out the presence of an insulinoma. Thus, there remains a continuing important back-up role for arterial calcium stimulation venous sampling studies. Semiquantitative analysis of pancreatic Exendin uptake (SUVmax) may not distinguish between normal, diffuse NIPHS and PGBH patients.

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Figure legends:

Figure: 1 The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 3 show the site of a pancreatic uncinate insulinoma only on the PET component. However it was identified on an outside contrast CT.

Figure: 1a (Supplementary). The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 4 show the site of a pancreatic body insulinoma only on the PET component. However, it was identified on an outside Contrast CT.

Figure: 1b (Supplementary). The transaxial co-registered PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) obtained from patient 6 show the site of a pancreatic tail insulinoma only on the PET component. This patient had a negative outside contrast CT study.

Figure 2: The transaxial co-registered (PET & CT (A.), CT (B.), PET (C.) and maximum projection images (D.) in patient 11 with proven nesidioblastosis, show relatively uniform Exendin uptake throughout the pancreas, a normal coregistered CT and a normal outside contrast CT. The pancreatic SUVmax measured in this case was 10.

Table 1: Clinical details of 20 EHH patient scans

pt no	age (yrs)	relevant history	symptom description & duration	(yrs)	Fasting	PPH
1	14		Seizures in morning	0.5		
2	30		Sweats, slurred speech	7		
3	66		Headache, blurred vision	1.5		
4	66		Collapsed: hypoglycaemia	0.2	+ve	
5	82	NIDDM diet	Confusion, vision loss	3	+ve	
6	33		Confusion, anxiety	0.5		
7	50		Collapse: Unaware hypo	0.2		
8	58		Confusion, sweats,	1.6	+ve	
9	64	Prior NIDDM	Tremors, sweats, drowsy	1	+ve	
10	66	Fundoplication 1991, 2015	Blurred vision, sweats	3	-ve	+ve
11	37	Bariatric surgery 2014	Blackouts	2		+ve
12	23	Obesity, mother had NIPHS as 6y/0	Sweats, hunger, unaware	0.3	+ve	
13	60	Occult insulinoma, post-surgery	Seizures, confusion	28		
14	60	fundoplication, alcohol, Sarcoid	Tremor, sweats, collapse	l0.5	-ve	
15	74	Prior NIDDM,	Dementia ? symptoms			
18	69	CVD	Confusion/collapse	1		+ve
19	52	Bariatric surgery '95,'00,'12	Dizziness, sweats	6	-ve	+ve
20	26	Epilepsy (on Epilim)	Neuroglycopenic	0.8	-ve	
21	71	CVD, CRF, Cushing's, NIDDM	Unstable angina, drowsy	0.5		
24	37	8 Co-morbidities, hypoglycaemia	Syncope, sweating	2	-ve	+ve
10	67	Relapse post-surgery	Blurred vision, sweats	0.6		

NIDDM. non-insulin dependent diabetes mellitus, CVD: Cardiovascular disease, +ve: positive
Fast: 72 hr fasting study, -ve: negative, +/-: equivocal, PPH: post prandial hypoglycaemia
CRF: chronic renal failure, EHH: endogenous hyperinsulinaemic hypoglycaemia

Table 2: Imaging, treatment and outcomes in patients with EHH

Pt No	Other tests	GLP-1 lesion Location	Final Diagnosis	treatment & status at April 2020	
A) Patients treated surgically					
1	CT+/-	Body/tail	Insulinoma	Enucleation	Cured
2	CaS+ CT+	Body/tail	Insulinoma	Distal	Cured
3	CT+ SSR-	Uncinate	Insulinoma	Duod	Cured
4	CT+ SSR-	Body	Insulinoma	Duod	Cured
5	CaS+ CT- EUS+ SSR+ ^	Nil*	Insulinoma	Laparoscopic	Cured
6	**CaS+ CT- IOUS+**	Uncinate	Insulinoma	Distal	Cured
7	CT+ MRI+ SSR+(tail)**	Uncinate	Insulinoma	Duod	Cured
8	CaS- CT- MRI- EUS+	Tail	Insulinoma	Distal	Cured
9	CT & MRI: splenunculus	Extra pancr	Insulinoma	Laparoscopic	Cured
10	CaS+** CT+ **	Uncinate**	PGBH	Duod #50%	Recurred: 0.7 yrs
11	CT- MRI-	Diffuse	PGBH	Distal #67%	Recurred: 0.5 yrs
12	CaS+ Tail CT- EUS-	Diffuse	NIPHS	Distal	Recurred :1.5 yrs
B) Non-operative patients					
13	CT- EUS- SSR- US-	Uncinate	Insulinoma	Refused surgery, well on diazoxide	
14	CT+,(tail) FDG- SSR-	Diffuse	PGBH	Stable on diazoxide, off alcohol	
15	CT- EUS-	Diffuse	Unknown	Lost to follow-up soon after scan	
18	CT- SSR- Ins ab: +ve	Diffuse	Autoimmune	Cured on stopping clopidogrel	
19	CT- SSR-	Diffuse	PGBH	Creon and jejunal feeds	
20	CT- EUS-	Diffuse	MDM: Nesid	Well controlled on diazoxide	
21	CT- MRI- SSR-	Diffuse	CRF,	Still well after stopping diazoxide	
24	CT- EUS- FDG- SSR-	Diffuse	?NIPHS	Therapy: no better, refused surgery	
10	CT- MRI- SSR-	Diffuse	PGBH	Better on diazoxide & jejunostomy	

pancr: pancreatic, Duod: duodenopancreatectomy, Distal: distal pancreatectomy, EUS: endoscopic ultrasound , CaS: calcium stimulation, IOUS: intraoperative US, *: false negative, **: false positive, ^: positive on retrospective review, MDM: multidisciplinary meeting, Nesid: nesidioblastosis, #: extent of pancreatic resection, Insab: insulin antibodies. , CRF: chronic renal failure.

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Table 3 Pancreatic Exendin SUVmax in PGBH pts

pt no	relevant clinical details	72 hr Fast	Reader 1 SUVmax	Reader 2 SUVmax
10	Fundoplication 1991, 2015	-ve	5	4.9
11	bariatric surgery		9.8	10
14	fundoplication, alcohol, Sarcoid	-ve	8.7	8.7
19	gastric bypasses x3, jejunostomy	-ve	6.2	5
10	relapse post-surgery		6.8	6.2
	SUVmax:	mean	7.3	7.0
		S.D.	1.9	2.3

Table 1 (supplementary) Exendin scan details

Pt no	Weight (Kg)	Ga68 dose (MBq)	Uptake (min)	Exendin symptoms	Glucose baseline	(mM/L) nadir	Glucose given
1	59	138	81	N&V	5.9	3.4	IVR
2	107	105	79	N	4.9	2.8	IV
3	79	87	62		7.9	5.2	IVR
4	102	216	60		3.7	3.7	IVR
5	52	128	81		4.4	2.6	O & IV
6	68	41	51		5.3	2.6	IVR
7	138	88	85		2.9	2.9	IVR
8	69	148	74	N&V	5.2	3.4	oral
9	131	288	118	N&V	5.8	3.9	oral
10	77	145	81	N	8.1	4.1	IV R
11	68	70	78	N	5.5	3.8	O & IV
12	151	140	85		4.7	2.7	IVR
13	92	87	67		4.1	2.1	IV
14	91	226	60		7.1	2.7	O & IV
15	38	96	76		5	3.5	IV
18	66	207	95		3.4	3.2	IVR
19	56	68	75	N	2.9	4.9	No
20	77	174	62	N&V	6.6	3.4	IV
21	71	111	60		3.8	2.9	IV
24	63	180	85		4.8	4.3	IV
10	77	145	81	N&V	7.8	5.1	IVR

N: nausea; V: vomiting, IV: Intra-venous glucose during Exendin uptake.
IVR: IV glucose running before Exendin was given.

Table 2 (supplementary) : Details of surgical findings

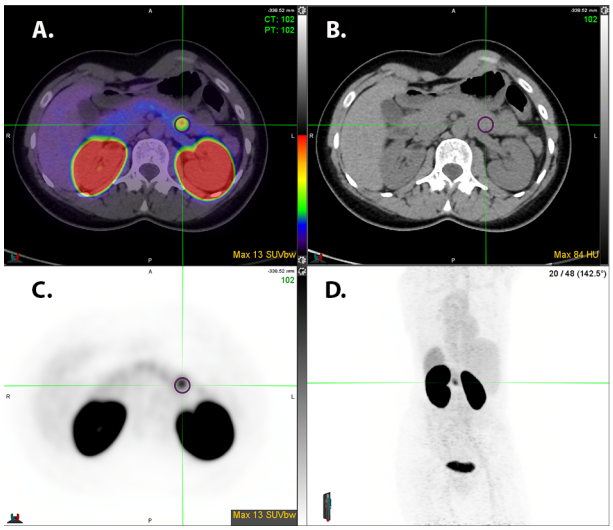
Pt No	GLP-1 diagnosis	GLP-1 lesion location	Tumour site at surgery	Tumour size (mm)	Tumour K-67
1	Insulinoma	Body/tail	Same	12	<1%
2	Insulinoma	Body/tail	Same	13x3x15	<2%
3	Insulinoma	Uncinate	Same	18x15x15	1%
4	Insulinoma	Body	Same	21	1%
5	Diffuse*	Nil*	Tail	11x6	
6	Insulinoma	Tail	Same	9x7	<1%
7	Insulinoma	Uncinate	Same	21	<2%
8	Insulinoma	Tail	Same	13x14	
9	Insulinoma	Extra pancreatic	Same	15x10x10	<1%
10	Insulinoma**	Uncinate**	Same		
11	Diffuse	Diffuse	Nesid		
12	Diffuse	Diffuse	Nesid		

*: false negative, **: false positive; Nesid: nesidioblastosis.

Table3 (supplementary) : Reader concordance and accuracy

Pt no	Reader 1: SUVmax lesion	Correct	Reader 2: SUVmax lesion	Correct	Readers Agree	Cohen's Kappa Reader Agreement +ve	-ve	Only Reader 2 +ve
1	10.6	1	10.6	1	1	1		
2	23.6	1	24.0	1	1	1		
3	12.4	1	12.4	1	1	1		
4	24.3	1	24.0	1	1	1		
5					1	1		
6	14.0	1	14.0	1	1	1		
7	17.0	1	17.0	1	1	1		
8			6.7					1
9	24.3	1	24.0	1	1	1		
10		1	7.3	1				1
11		1		1	1		1	
12		1		1	1		1	
13	14.0	1	14.0	1	1	1		
14		1	8.7					1
15		1		1	1		1	
16		1		1	1		1	
17		1		1	1		1	
18		1		1	1		1	
19		1		1	1		1	
20		1	6.9					1
21		1		1	1		1	
22		1		1	1		1	
23		1		1	1		1	
24		1		1	1		1	
10		1		1	1		1	
Total correct		23		21	21	8	13	4

Reader agreement= 83%, Cohens Kappa= 0.65 ie suggests substantial agreement.
Lesion: SUVmax of potential insulinoma



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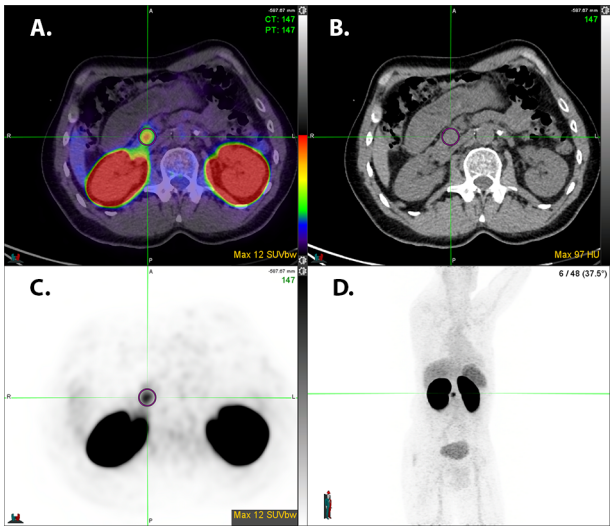

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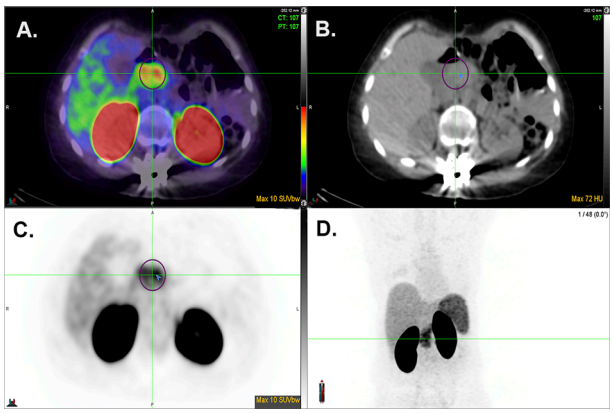

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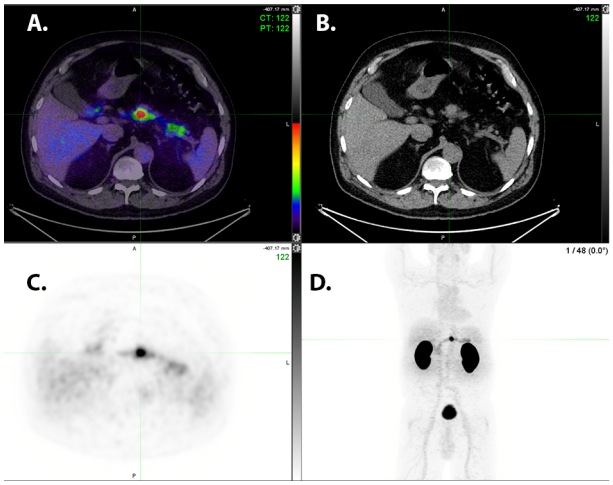

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