Novel PET tracer $^{68}$Ga-DOTATATE PET/CT can be alternative imaging method in patients with insulinomas

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$^{68}$Ga-DOTATATE PET/CT in insülinoma
**Summary:** Insulinomas are the most common cause of hypoglycemia resulting from endogenous hyperinsulinism. The diagnosis of insulinoma is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycaemia. Most of the insulinomas are islet-cell tumors. They are often small (less than 2 cm), benign, and difficult to localize with current imaging techniques. The non-invasive procedures such as transabdominal ultrasonography, spiral computed tomography (CT), magnetic resonance imaging (MRI), $^{111}$-In-pentetreotide imaging, fluorine-18-L-dihydroxyphenylalanine positron emission tomography ($^{18}$F-DOPA PET) and invasive procedures such as endoscopic ultrasonography or a selective arterial calcium stimulation test (SACST) with hepatic venous sampling can be used to show insulinomas. In this case report we used novel PET tracer $^{68}$Ga-DOTATATE PET/CT for three patients with insulinoma. All patients’ insulinomas were shown clearly with $^{68}$Ga-DOTATATE PET/CT. $^{68}$Gallium-DOTATATE PET/CT imaging may be a useful and non-invasive imaging technique to localized insulinomas preoperatively.

**Key words:** $^{68}$Ga-DOTATATE PET/CT, insulinoma, neuroendocrine tumor

**Introduction:** The common clinical manifestation of an insulinoma is fasting hypoglycemia, and neuroglycopenic symptoms. The diagnosis of insulinoma is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycemia (72-hour fast). Virtually all insulinomas are islet-cell tumors; after biochemical diagnosis, imaging techniques are then used to localize the tumour. Accurate preoperative localization of an insulinoma is desirable because some tumours may not be palpable at the time of surgery (1). The non-invasive procedures available include transabdominal ultrasonography, spiral computed tomography (CT), magnetic resonance imaging (MRI), $^{111}$-In-pentetreotide imaging, and fluorine-18-L-dihydroxyphenylalanine positron emission tomography ($^{18}$F-DOPA PET). Positron emitting radiopharmaceuticals for somatostatin receptor (SSTR) imaging, DOTA analogues, which include $^{68}$Gallium-DOTA-D-Phe-Tyr3-octreotate(DOTATATE), $^{68}$Gallium-DOTA-D-Phe-Tyr3-octreotid (DOTATOC), and $^{68}$Gallium-DOTA-1-Nal(3)-octreotid (DOTANOC), have a high affinity to SSTR, especially to SSTR2. Recently, several studies have demonstrated that $^{68}$Gallium-labeled somatostatin analogue positron emission tomography (PET) when combined with CT has a higher sensitivity for detecting
NETs than SSTR scintigraphy. A meta-analysis study suggested that $^{68}$Gallium-DOTATATE was most accurate for detecting NETs (6=2). In this study we review our patients with insulinoma and discuss usefulness of $^{68}$Gallium DOTATATE PET/CT as a first choice imaging method.

**Case 1:** A 49-year-old woman was referred for evaluation of repeated episodes of hypoglycemia symptoms and weight gain. Capillary glucose measured by health professional was 47 mg/dl, and she improved after intravenous glucose administration.

After fasting for 10 hours, she became diaphoretic and confused. Serum values at that time were as follows: Glucose: 44 mg/dl, Insulin: 22.3 microU/ml, C-peptide: 3.06 ng/ml. Spiral CT of the abdomen revealed mass at the body of pancreas. $^{68}$Gallium-DOTATATE PET/CT showed a lesion at the body of the pancreas (figure 1). The location of the tumor was confirmed by intraoperative ultrasonography. The patient underwent enucleation of the insulinoma. Pathologic examination confirmed insulinoma.

**Case 2:** Fifty-nine-year-old woman complained headache, sweating. After fasting for 6 hours, she became hypoglycemic symptoms. Serum values at that time were follows: Glucose: 53 mg/dl, Insulin: 37 microU/ml, C-peptide: 4.14 ng/ml. Spiral CT of the abdomen the patient had no visible mass. $^{68}$Gallium DOTATATE PET/CT showed a lesion at the body of pancreas(figure 2). Oral diazoxide was started and operation was planned.

**Case 3:** A 55-year-old woman had complain headache. After fasting for 12 hours, she became hypoglycemic. Serum values at that time were follows: Glucose: 36 mg/dl, Insulin: 11.43 microU/ml, C-peptide: 2.32 ng/ml. Spiral CT of the abdomen not visible mass. $^{68}$Gallium DOTATATE PET/CT showed a lesion at the tail of the pancreas(figure 3). The location of the tumor was confirmed by intraoperative ultrasonography. The patient underwent distal pancreatectomy. Pathologic examination confirmed insulinoma.

**Discussion:** In this study all of our patients have fasting hypoglycemia. Seventy two-hour fasting test was performed to all patients. All the patients have inappropriately high serum insulin concentrations during 72-hour fast so, insulinomas were diagnosed. After
biochemical diagnosis, imaging techniques were used to localize the tumour. Accurate
preoperative localization of an insulinoma is desirable because some tumours may not be
palpable at the time of surgery (1). The non-invasive procedures available include spiral
computed tomography (CT), magnetic resonance imaging (MRI), transabdominal
ultrasonography, 111-In-pentetreotide imaging, and 18F-DOPA PET. Our patients have
biochemically proven insulinomas but non-invasive procedures were able to show only
one of three insulinoma patients. In patients with established insulinoma and negative
non-invasive radiologic localization studies, endoscopic ultrasonography or SACST with
hepatic venous sampling can be performed to localize the tumour. These procedures are
invasive and skills person are necessary. The choice of procedure depends upon which
tests is available and local radiologic skill. In our centre we have no opportunity to use
invasive procedures (endoscopic ultrasonography or SACST with hepatic venous
sampling). The majority of neuroendocrin tumors (NETs) express SST receptors, so they
can be effectively targeted and visualized with radiolabelled SST analogues in vivo.
Pentetreotide scintigraphy can be used to localized the insulinomas but 40 percent of
insulinomas will be missed with these method.

Most of the studies have demonstrated the potential of PET technology using $^{68}$Gallium-
DOTA-TOC, $^{68}$Gallium-DOTA-NOC and $^{68}$Gallium-DOTA-TATE. In particular PET
clearly offers higher resolution and improved pharmacokinetics as compared to SST
receptor scintigraphy, with promising results for the detection of SST receptor-expressing
tumours and provides prognostic information (13). Recently, PET with the $^{68}$Ga-DOTA-
conjugated peptides $[^{68} \text{Ga-DOTA0-Tyr3}]$ octreotide ($^{68}$Gallium-DOTA-TOC),
$[^{68} \text{Ga-DOTA0-1NaI3}]$ octreotide ($^{68}$Gallium-DOTA-NOC) and $[^{68} \text{Ga-
DOTA0-Tyr3}]$ octreotate ($^{68}$Gallium-DOTA-TATE) has brought about dramatic
improvements in spatial resolution. These agents are increasingly being used in
specialized centres. $^{68}$Gallium-DOTA-TOC, $^{68}$Gallium-DOTA-NOC and $^{68}$Gallium-
DOTA-TATE can all bind to SST receptor 2 but they have different affinity profiles for
other SST receptor subtypes. In particular, $^{68}$Gallium-DOTA-NOC also shows a good
affinity for SST receptors 3 and 5, $^{68}$Gallium-DOTA-TOC also binds to SST receptor 5. $^{68}$Gallium-DOTA-TATE has a predominant affinity for SST receptor 2. A study demonstrated that somatostatin receptors 2 and 5 are the major somatostatin receptors in expressed in insulinomas. These findings suggest that $^{68}$Gallium-DOTATATE has high affinity for SSTR2 and SSTR5 and thus when positive in a biochemically proven patient, are specific for insulinomas as observed in our patient. It has been previously reported that $^{68}$Gallium-DOTATATE PET/CT can detect NETs as small as 6 mm. $^{68}$Gallium-DOTATATE PET/CT can be helpful to localized small insulinomas.

In the literature there were case report about using of $^{68}$Gallium-DOTATATE PET/CT as an imagining method to detect insulinomas. Both studies were able to show successfully insulinoma of the patients (3,4). In our study, all patients’ insulinomas were shown clearly with $^{68}$Gallium-DOTATATE PET/CT. In a study conducted by Prasad et al., It was observed that tumor localization was compatible with DOTATATE in patients with insulinoma(5). In a study by Pavel et al., The localization accuracy of pathologically proven patients with $^{68}$Gallium-DOTATATE PET/CT insulinoma(6)

**Conclusion:** $^{68}$Gallium-DOTATATE PET/CT can be alternative method for the patient with negative non-invasive radiologic localization studies. This imaging method can be alternative to the invasive method such as selective arterial calcium stimulation test. To our knowledge, this one of the first attempts to detects insulinomas by use of novel PET tracer $^{68}$Gallium-DOTATATE PET/CT. Other big studies confirmed our results were necessary.

Written informed consent was obtained from all patients.
References:


6- Pavel Nockel, et al. Localization of Insulinoma Using 68Ga-DOTATATE PET/CT ScanThe Journal of Clinical Endocrinology & Metabolism; Copyright 2016 DOI: 10.1210/jc.2016-3445
Figures

Figure 1: $^{68}$Gallium DOTATATE PET/CT showed a lesion at the body of pancreas (case 1)

Figure 2: $^{68}$Gallium DOTATATE PET/CT showed a lesion at the body of pancreas (case 2)
Figure 3: 68Gallium DOTATATE PET/CT showed a lesion at the tail of the pancreas (case 3)