

## Case Report

# Calcium Stimulation Test for Insulinoma Localization in an End-stage Renal Disease Patient on Diazoxide

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## Abstract

Insulinomas are rare, and even rarer in patients with end-stage renal disease (ESRD). Clear criteria for the biochemical diagnosis of insulinomas in patients with renal failure have not been established, and hypoglycemia is often attributed to the renal disease itself, frequently leading to a delay in diagnosis. We describe a case of a patient who presented with asymptomatic recurrent hypoglycemia during hemodialysis. Disease progression and biochemical testing strongly suggested an insulinoma. Computed tomography (CT) of the abdomen and pelvis, <sup>111</sup>In-pentetreotide scintigraphy and endoscopic ultrasound did not localize a pancreatic tumor. A calcium stimulation test was performed while the patient was taking diazoxide due to severe hypoglycemia with fasting for a couple of hours without treatment. The test showed a marked increase in insulin after calcium infusion in the dorsal pancreatic artery, localizing the tumor to the body and tail of the gland. Exploratory surgery easily identified a tumor at the body of the pancreas and pathology confirmed an insulin-secreting pancreatic neuroendocrine tumor. On follow-up, there was resolution of the hypoglycemia. We review the challenges of diagnosing an insulinoma in ESRD and describe a successful intra-arterial calcium stimulation test done in an ESRD patient while continuing diazoxide.

**Key Words:** insulinoma, diazoxide, calcium stimulation test, end stage renal disease

Insulinomas, while being the most common functioning islet cell tumors, are rare with an incidence of 4 per million persons [1]. They are exceedingly rare in patients with end-stage renal disease (ESRD), reported in just 7

patients, including 3 patients on hemodialysis and 1 patient on peritoneal dialysis [2–8]. Establishing the diagnosis of insulinoma is always challenging [9], and even more so in ESRD, where spontaneous hypoglycemia can be due to

other factors, including decreased renal gluconeogenesis, impaired insulin clearance, decreased hepatic gluconeogenesis from uremia, an abnormal counter-regulatory hormone response, and malnutrition [2]. Hypoglycemia in ESRD is often attributed to these other causes, leading to missed or delayed diagnosis in cases of an insulinoma.

Once diagnosed, insulinomas are often difficult to localize. Several strategies exist for localizing difficult-to-find tumors, including intra-arterial calcium administration to arteries supplying the pancreas to stimulate insulin secretion from the tumor. Diazoxide, a potassium channel activator used to treat hyperinsulinemia, is usually discontinued during this testing so as not to suppress the insulin response to calcium. We report the first case of successful insulinoma localization from a calcium stimulation test performed in a patient with ESRD while continuing diazoxide.

## Case Report

A 36-year-old man with ESRD due to systemic lupus erythematosus (SLE) and hypertension, on hemodialysis for 5 years, was referred to the San Francisco General Hospital Endocrine Clinic for recurrent hypoglycemia. During the previous 10 months, the patient was noted to have hypoglycemia on multiple occasions during hemodialysis with nonfasting serum blood glucoses (BG) ranging from 30 to 40 mg/dL. He denied symptoms other than weakness during these episodes. A cortisol level obtained during 1 instance of hypoglycemia (BG 34 mg/dL) was 14.7 mg/dL, which, given the degree of hypoglycemia, suggested possible adrenal insufficiency. His medications were benazepril 20 mg daily and cinacalcet 30 mg daily. He did have a history of prior prednisone use for many years for his SLE, but he had not been taking it for at least several months prior to presentation. There was no family history of endocrine disorders.

The patient was admitted to the hospital for a supervised fast. Physical examination was unremarkable. After 4.5 hours of fasting he became confused, diaphoretic, and irritable. Blood glucose was 27 mg/dL. Symptoms resolved with treatment of the hypoglycemia, thus establishing Whipple's triad. When BG was 27 mg/dL, other labs included insulin 19.8  $\mu$ U/mL (ref 3–25), C-peptide 7.6 ng/mL (ref 0.8–3.5), proinsulin 385.5 pmol/L (ref < 26.8), and beta-hydroxybutyrate 0.07 mmol/L (ref < 0.28). Sulfonylurea panel and insulin autoantibody were negative. These results are typically diagnostic of an insulinoma (criteria: BG < 55 mg/dL, insulin  $\geq$  3.0  $\mu$ U/mL, C-peptide  $\geq$  0.6 ng/mL, proinsulin  $\geq$  5 pmol/L, and beta-hydroxybutyrate levels  $\leq$  2.7 mmol/L) [9]. However, in ESRD, endogenous glucose production, from both the kidney and liver, is reduced, contributing to fasting hypoglycemia. While insulin

secretion should be quickly suppressed with hypoglycemia, because of delayed insulin clearance in ESRD, insulin concentrations can remain elevated and further contribute to hypoglycemia. Unfortunately, no clear diagnostic criteria exist for appropriate insulin suppression in ESRD. For our patient, given his ESRD and possible mild adrenal insufficiency (discussed below), the diagnosis of an insulinoma remained uncertain.

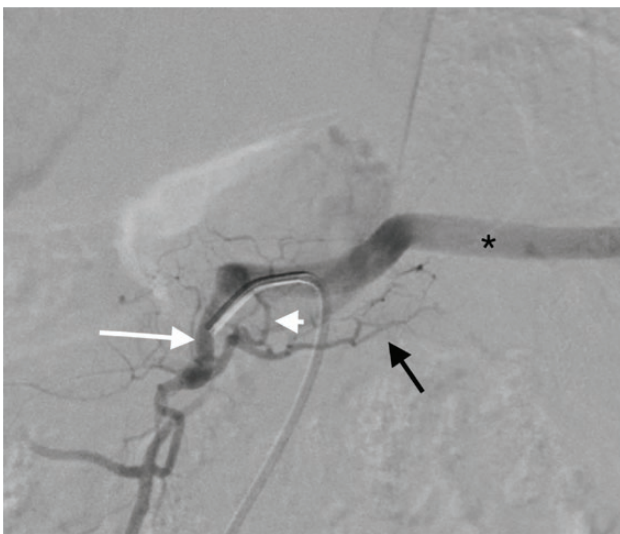
During hospitalization the patient had a cosyntropin stimulation test that showed a precortisol level of 8.5 ug/dL, with an adrenocorticotropic hormone (ACTH) level of 55 pg/mL (ref 7–69 pg/mL; Siemens Immulite Assay; Siemens, Malvern, PA) and a postcortisol level of 15.8 ug/dL. This was deemed an insufficient response, especially in the setting of recurrent hypoglycemia. A 21-hydroxylase antibody test was negative and an abdominal computed tomography (CT) scan did not identify a pancreatic islet-cell tumor. He was therefore discharged home on hydrocortisone and diazoxide, with resolution of his hypoglycemic episodes. Repeat cosyntropin stimulation testing was performed on him as an outpatient 8 months later, with a precortisol level of 16.1 ug/dL and a postcortisol level of 20.3 ug/dL. It was presumed the patient had recovered from possible adrenal suppression from prior high-dose glucocorticoid use and hydrocortisone was subsequently discontinued. Further imaging with an octreotide scan and endoscopic ultrasound was performed and did not localize a pancreatic tumor. The patient refused referral for surgical exploration and did not follow-up further with endocrinology for several years.

As a side note, subsequent repeat ACTH several years later, again with the Siemens Immulite assay, was 236 pg/mL, with a corresponding cortisol of 16.8 ug/dL. This result was considered spurious given the cortisol and low clinical suspicion for adrenal insufficiency at the time. He had remained off prednisone and hydrocortisone. Subsequently, after it was reported that the Siemens Immulite ACTH assay could cause erroneously elevated results [10], this was rechecked using the Roche Cobas ACTH assay (Roche Diagnostics, Mannheim, Germany). The ACTH was actually borderline low at 5.4 pg/mL (ref 7.2–63.3 pg/mL), with a corresponding cortisol of 12.7. This suggests the original ACTH readings had been erroneously high and the patient may have initially had some degree of mild adrenal dysfunction due to his prior glucocorticoid use, which resolved with time.

Two years after his initial evaluation, the patient re-presented to the endocrine clinic with worsening hypoglycemia and frequent emergency room visits for nocturnal hypoglycemia with loss of consciousness. He also had a 50-pound weight gain due to eating and drinking soda every 4 hours. He had self-increased his diazoxide to

150 mg at night with minimal improvement in symptoms. Repeat endoscopic ultrasound and CT abdomen pelvis did not reveal a pancreatic lesion.

To localize the insulinoma, an intra-arterial calcium stimulation test was performed. Due to a hypoglycemic episode to 30 mg/dL while fasting in preparation for a CT scan, it was deemed unsafe to discontinue diazoxide during the calcium stimulation test. The patient fasted for 12 hours but took diazoxide 150 mg the night before and 50 mg on the morning of the procedure. The gastroduodenal, proper hepatic, superior mesenteric, and dorsal pancreatic arteries were catheterized with calcium gluconate bolused into each artery. Blood samples from the right hepatic vein were obtained at baseline and at 30, 60, 90, 120, and 150 seconds after injection. Notably, the majority of the blood supply to the body and tail of the pancreas was identified on angiography to originate from the dorsal pancreatic artery rather than branches from the splenic artery, as is more typically seen (Fig. 1). The results of the intra-arterial calcium stimulation showed a step-up in insulin from a baseline of 7.2  $\mu$ U/L to a peak of 886.7  $\mu$ U/L 90 seconds after injection of the dorsal pancreatic artery (Fig. 2). Injection in the other arteries showed no significant increase. The capillary BG decreased to 36 mg/dL with the surge in insulin. The patient reported tremors and diaphoresis and intravenous glucose (25 gm) was administered, with improvement in his symptoms. He was monitored postprocedure and his BG remained low at 44 mg/dL 4 hours later, likely due to the very high insulin level from the stimulation test



**Figure 1.** Visceral arteriogram demonstrates the tip of the catheter in the dorsal pancreatic artery (long white arrow). In this patient, the dorsal pancreatic artery is the dominant supply to the neck and body of the pancreas via the pancreatica magna artery (short white arrow) and transverse pancreatic artery (black arrow). Contrast is seen refluxing in the splenic artery (asterisk), which does not show significant supply to the pancreas.

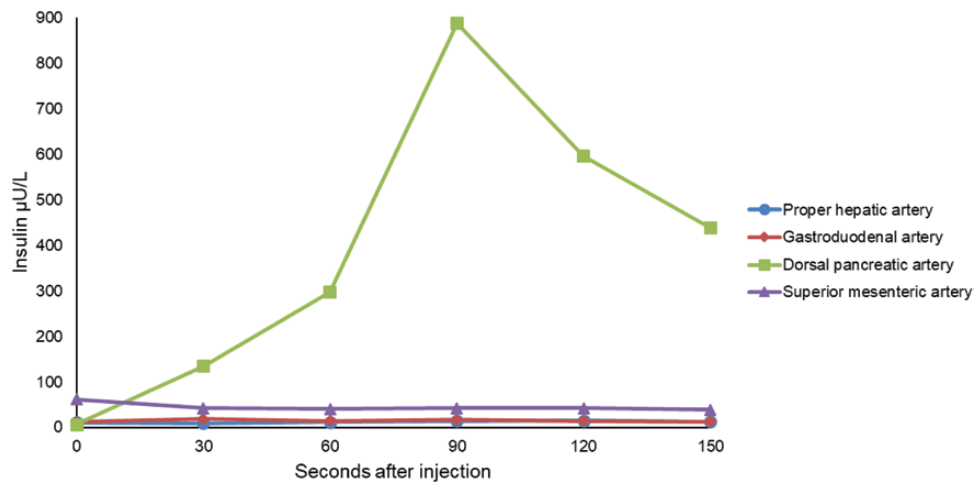
and slow insulin clearance due to his renal failure. He was given an additional 25 grams of intravenous glucose and food, and his BG rose to 118 mg/dL. He refused to remain in the hospital and left against medical advice.

The patient was referred to surgery for exploration and presumed resection of the distal pancreas. While awaiting surgery, whole body  $^{68}$ Gallium ( $^{68}$ Ga)-DOTATATE (a radioconjugate with a high affinity to somatostatin receptor 2 positron emission tomography (PET)/CT scan [11]) became available under a research protocol. A radiotracer avid lesion was seen at the level of the body of the pancreas measuring 1.6  $\times$  1.4 cm with a standardized uptake value of 32.2 (Fig. 3). Surgical laparoscopic exploration revealed an easily identifiable tumor situated directly over the body of the pancreas, and the patient underwent a distal pancreatectomy. Pathology showed a 1.9  $\times$  1.2  $\times$  1.2 cm well-differentiated tumor, with immunohistochemical staining positive for insulin, synaptophysin, chromogranin and a weak, patchy cytokeratin cocktail consistent with a low-grade insulin-secreting pancreatic neuroendocrine tumor. Postoperatively, the patient's BG normalized with resolution of hypoglycemic symptoms and significant improvement in his quality of life. Notably, he lost 60 pounds 5 months postoperatively.

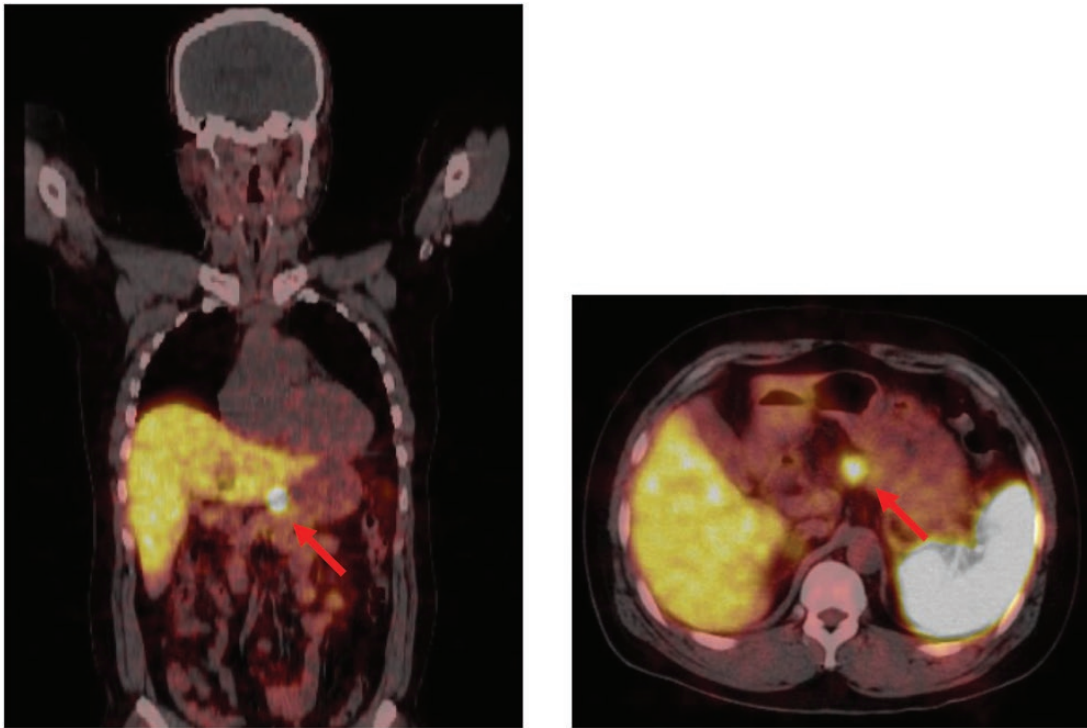
## Discussion

Spontaneous hypoglycemia in ESRD is multifactorial and may occur due to reduced renal gluconeogenesis, decreased insulin clearance, reduced hepatic gluconeogenesis, impaired counterregulatory hormone response, diminished caloric intake, and the use of high glucose-containing dialysate during hemodialysis or peritoneal dialysis [2]. Thus, the diagnosis of endogenous hyperinsulinemia in the presence of ESRD is difficult and may be delayed without established criteria in this setting. Our patient had documented Whipple's triad, though this can be seen in renal failure without the presence of an insulinoma. The clinical progression of his symptoms over several years with significant weight gain increased our suspicion for insulinoma. He initially responded well to diazoxide but 2 years later, re-presented with symptomatic hypoglycemia despite more aggressive diazoxide treatment.

As is common with insulinomas, initial localizing studies were negative. In these cases, an intra-arterial calcium stimulation test is reported to localize 88% to 100% of insulinomas to the correct region of the pancreas [11]. Understanding the arterial supply of the pancreas is important. Interestingly, in this case the patient displayed variable anatomy. His angiography showed no significant arterial supply to the pancreas from the splenic artery, which is normally the dominant blood supply to the body



**Figure 2.** Insulin in hepatic vein over time following arterial calcium gluconate stimulation.



**Figure 3.** Whole body  $^{68}\text{Ga}$ -DOTATATE showing a radiotracer avid lesion at the level of the body of the pancreas measuring  $1.6 \times 1.4$  cm, with a standardized uptake value (SUV) of 32.2 (red arrow).

and tail of the pancreas. Rather, supply to this region appeared to originate from the dorsal pancreatic artery, which was selectively catheterized and bolused with calcium gluconate, along with the gastroduodenal, proper hepatic, and superior mesenteric arteries.

In pancreatic  $\beta$ -cells, glucose enters the cell and generates adenosine triphosphate (ATP), which closes the potassium ATP ( $K_{\text{ATP}}$ ) channels. Cells are depolarized, voltage gated calcium channels open, and increased intracellular calcium leads to insulin release. Sulfonylureas bind to the  $K_{\text{ATP}}$  channels and also close them, thereby increasing

insulin secretion. However, diazoxide opens the  $K_{\text{ATP}}$  channels, hyperpolarizing the cell, leading to the closure of voltage gated calcium channels, decreased intracellular calcium, and inhibition of insulin secretion. Thus, diazoxide is especially useful in the management of hyperinsulinism from an insulinoma [12]. However, in a patient undergoing a calcium stimulation test, calcium enters the pancreatic beta cells primarily through the voltage-activated calcium channels closed by diazoxide. In the presence of diazoxide, it would therefore be expected that insulinoma cells would be unresponsive to the increase in extracellular calcium.



Accordingly, protocols for the calcium stimulation procedure dictate that diazoxide should be discontinued at the time of testing so as not to suppress insulin secretion.

For safety reasons, our patient was maintained on diazoxide, including on the morning of the test. This is the first report, to our knowledge, of a successful intra-arterial calcium stimulation test while continuing diazoxide treatment. Our patient showed marked elevation in insulin after calcium infusion into the dorsal pancreatic artery, localizing the tumor to the body and tail of the gland, which corresponded to the tumor location at surgery. A previous study reported a false-negative selective arterial calcium stimulation in a patient maintained on diazoxide, and repeat testing in the same patient after diazoxide was discontinued and localized the insulinoma [13]. The reason for success with diazoxide in 1 patient but not the other is likely due to underlying differences in the tumors. It was first observed over 30 years ago that there are striking differences in insulinoma responsiveness to diazoxide [14]. Different subtypes of insulinomas have been proposed with different postulated mechanisms responsible for dysregulated insulin secretion [15]. Therefore, we hypothesize the tumor in our patient was relatively unresponsive to diazoxide. Patients with diazoxide-unresponsive tumors also tended to have relatively higher proinsulin concentrations, as was the case in our patient [14]. Unresponsiveness to diazoxide is further supported by the severe hypoglycemia requiring frequent eating despite treatment. All of these factors may have allowed for successful arterial calcium stimulation, though future studies will be needed to determine how best to identify patients who can have successful tumor localization while still taking diazoxide.

Of note, had it been available earlier,  $^{68}\text{Ga}$ -DOTATATE PET/CT would also have revealed the tumor location, foregoing the need for calcium stimulation.  $^{68}\text{Ga}$ -DOTATATE PET/CT identifies most insulinomas with better accuracy than CT, magnetic resonance imaging (MRI), ultrasound, and octreotide scintigraphy [16]. Therefore, while selective arterial secretagogue injection remains more accurate for regionalizing insulinomas [17], it may be used much less frequently.  $^{111}\text{In}$ -DTPA-exendin-4 SPECT/CT, used for glucagon-like-peptide-1 receptor imaging, is also known to be a more sensitive modality for the localization of insulinomas compared with traditional imaging methods.

Our case highlights that in ESRD, there will be a significant risk for prolonged postprocedure hypoglycemia given a delay in clearance of the very high circulating insulin concentrations. In our patient, this hypoglycemia risk lasted at least 4 hours. Given he left against advice, we don't know how much longer this may have lasted. Postprocedural-prolonged hypoglycemia in ESRD should be anticipated and patients should be monitored for many

hours postprocedure. Consideration of overnight observation may be appropriate.

This case shows that while diazoxide is traditionally not used with an intra-arterial calcium stimulation test, it can be continued in some cases of severe hypoglycemia with successful results. Insulinoma in the setting of ESRD is rare and difficult to diagnosis, often leading to a delay in treatment. It is important to note that clearance of insulin after the calcium stimulation may be slow and patients need to be closely monitored for a prolonged period postprocedure to ensure that glucose levels are stable.

## Additional Information

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**Data Availability:** Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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