



## The use of selective arterial calcium stimulation test in the diagnosis of the hyperinsulinemic hypoglycemia

Yasemin Aydoğan Unsal<sup>a,\*</sup>, Ozen Oz Gul<sup>b</sup>, Soner Cander<sup>b</sup>, Coskun Ates<sup>b</sup>, Ensar Aydemir<sup>b</sup>, Oktay Unsal<sup>c</sup>, Canan Ersoy<sup>b</sup>, Erdinc Erturk<sup>b</sup>

<sup>a</sup>Yenimahalle Training and Research Hospital, Department of Endocrinology and Diseases of Metabolism, Ankara, Türkiye

<sup>b</sup>Uludağ University, Faculty of Medicine, Department of Endocrinology and Diseases of Metabolism, Bursa, Türkiye

<sup>c</sup>Gazi University, Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye

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#### Abstract

We examined the patients with hyperinsulinemic hypoglycemia who were performed non-invasive imaging techniques with doubtful or failed results. We compared the performances of the Selective Arterial Calcium Stimulation Test (SACST) and non-invasive imaging techniques. Eight patients with hyperinsulinemic hypoglycemia, performed SACST after evaluating with imaging modalities were examined retrospectively. Three patients were diagnosed with Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS), 4 with insulinoma, and 1 with autoimmune hypoglycemia after SACST. While the concordance between the SACST and surgery-proven pathology for insulinoma was 50% (2/4), the accuracy in the localization of insulinoma was 25%. Although SACST does not have high concordance with surgery-proven pathology and accuracy in the localization of insulinoma, it may be preferred in the differential diagnosis of hyperinsulinemic hypoglycemia in medical centers where other imaging techniques are not available, or in cases where other imaging methods obtain suspicious/inadequate diagnosis.



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### Introduction

Hypoglycemia is a rare disorder in patients who are not known to have diabetes and is diagnosed by low plasma glucose concentrations where symptoms and signs are relieved after plasma glucose levels rise [1]. Drugs, sepsis or other clinical illnesses, adrenal insufficiency, endogenous hyperinsulinism, or nonislet cell tumors are among the causes of hypoglycemia [2].

Differential diagnosis of hypoglycemia is based on history, physical findings, and laboratory data. When the etiology was unclear, plasma glucose, insulin, C-peptide, proinsulin, and beta-hydroxybutyrate concentrations should be measured. If hypoglycemia is not seen spontaneously, a fasting test or mixed meal test should be done. Furthermore, screening for the usage of oral hypoglycemic agents, observing the plasma glucose response to intravenous in-

jection of 1 mg glucagon, and measuring the insulin antibodies are recommended for seeking the etiology of hypoglycemia [3]. Hypoglycemia with plasma glucose concentrations below 55 mg/dl, trough insulin levels above 3.0 µU/mL, C-peptide levels above 0.6 ng/mL, and proinsulin levels above 5.0 pmol/L during a hypoglycemic episode β-hydroxybutyrate levels of 2.7 mmol/L or less and an increase in plasma glucose of at least 25 mg/dL (1.4 mmol/L) after intravenous glucagon confirm the diagnosis of endogenous hyperinsulinism. After diagnoses of endogenous hyperinsulinism with negative insulin antibodies, and negative screening for the usage of oral hypoglycemic agents localizing studies for insulinoma should be done [3].

Localizing studies include CT or MRI, transabdominal ultrasonography and EUS, somatostatin analogue-related imaging methods, and PET [4-6]. Although these imaging techniques may be used for tumour detection, they are not readily available in many medical centers and they are expensive. Furthermore, insulinomas less than 10 mm in diameter can be missed by non-invasive techniques [7]. In

\*Corresponding author:

Email address: [yaseminunsalay@gmail.com](mailto:yaseminunsalay@gmail.com) (Yasemin Aydoğan Unsal)

these cases, SACST with measurements of hepatic venous insulin levels after selective pancreatic arterial calcium injections can be helpful. Endoscopic ultrasonography is also helpful in these situations, but this technique is not available in all medical centres and is performed by a highly trained physician [8].

Selective Arterial Calcium Stimulation Test, first described by Doppman et al., was shown effective for localizing insulinomas of the pancreas [9]. Calcium, infused arterial vessels during the test, stimulates the release of insulin from tumour cells [10]. Some studies have suggested the superiority of SACST over non-invasive imaging studies for localizing an insulinoma. In the literature, the accuracy of SACST in localizing insulinomas has been found to range from 94% to 100% [11].

In this report, we intended to compare non-invasive imaging methods with SACST in the differential diagnosis of hyperinsulinemic hypoglycemia.

### Case Report

Eight patients admitted to the endocrinology clinic with the symptoms or/and signs of hypoglycemia between 2015 August and 2020 March and performed SACST after evaluating with variable imaging modalities were examined retrospectively. Hyperinsulinemic hypoglycemia was defined as a hypoglycemic event with high levels of plasma insulin and C-peptide at rest or during a fasting test. The non-invasive localization studies such as transabdominal ultrasonography, CT scan, and MRI of abdomen, and somatostatin receptor scintigraphy were done.

Selective Arterial Calcium Stimulation Test was performed after negative noninvasive imaging or negative EUS, equivocal lesion morphology or enhancement on noninvasive imaging modalities, Multiple Endocrine Neoplasia type-1 (MEN-1) patients with multiple (>1) pancreatic lesions on imaging.

Selective Arterial Calcium Stimulation Test was performed after 8 hours of fasting. A contrast agent was injected into the arterial supply of the pancreas, namely splenic, superior mesenteric, and gastroduodenal arteries for pancreatic arteriography by the same experienced interventional radiologist. Then femoral vein and artery cannulation were done. Ten percent calcium gluconate was injected into arteries at a dose of 0.025 mEq/kg via a catheter. After calcium injection, samples were taken via hepatic vein cannulation and sent to the laboratory for analysis. During the procedure, blood sugar was monitored by finger-sticks closely, and 5% dextrose was used to avoid hypoglycemia. The localization of the insulinoma in the head, body, or tail of the pancreas was estimated as an increase in insulin levels greater than 2-fold after injection of calcium gluconate at baseline, 30 s, 60 s, 90 s, 120 s, or 180 s.

After the SACST, a surgical procedure was planned after reviewing with general surgery at the council if the diagnosis or localization of the insulinoma was confirmed. In some patients, NIPHS was thought of as a diagnosis and medical treatment with diazoxide, octreotide, or both and in some cases, and partial pancreatectomy was planned. When the operation was planned with the diagnosis of insulinoma or NIPHS, intraoperative pancreatic ultrasonography was done to localize the lesions if the experienced

surgeon was present. Since the antibody test resulted too late in our medical center, the SACST was performed on 1 patient, and the patient was diagnosed with autoimmune hypoglycemia. Therefore, treatment with glucocorticoid was planned.

The study was conducted by the Declaration of Helsinki and the study was approved by the local ethics committee (Uludag University Faculty of Medicine Clinical Research Ethics Committee, Date: 11.08.2021 Decision no: 2021-11/14).

The Statistical Package for the Social Sciences software version 23 (SPSS) was used for the statistical analysis (IBM Corp; Armonk, NY, USA). The Chi square test analysis with the fourfold contingency table was used for evaluating the localizing pancreatic insulinomas and SACST and operative findings. The accuracy of SACST in localizing pancreatic insulinomas was retrospectively determined. Comparisons were also made between the SACST findings and operative findings.

A total of 8 patients (5 female, 3 male) who underwent SACST were examined in the study. The median age of the patients was 33 years (21-55). The baseline characteristics of the patients are shown in Table 1. Spontaneous hypoglycemia was seen in 5 patients, and levels of c-peptide and insulin were examined during hypoglycemia. However, in 3 patients hypoglycemia was shown after a prolonged supervised fast of <24 hours. All patients were examined with non-invasive imaging methods, also 1 patient was performed EUS. In our medical center, EUS was not performing, so the patient was admitted to another medical center for EUS by her voluntary decision (Table 2). Three patients were diagnosed with NIPHS, 4 with insulinoma, and 1 with autoimmune hypoglycemia after SACST.

In patient 1, after CT and MRI with negative findings as a cause of hypoglycemia, SACST was performed. The levels of insulin were increased after calcium infusion into pancreatic arteries at least two-fold from the baseline levels in the territory of Superior Mesenteric Artery (SMA). In the intraoperative USG, diffuse hyperplasia was seen, and the NIPHS was thought of as a diagnosis. In patient 2 and patient 7, CT was negative for insulinoma, so SACST was performed. The levels of insulin were increased in the territory of the Gastro-Duodenal Artery (GDA), SMA, and Splenic Artery (SPA). Verapamil/diazoxide was started with the diagnosis of NIPHS. Patient 3 with negative non-invasive imaging was performed SACST and the levels of insulin were increased 3 fold from baseline levels in the territory of SPA. The tumour was seen in the head of the pancreas during intraoperative USG contrary to SACST findings. In patient 4 with known MEN1, MRI showed a tumour in the head of the pancreas and during SACST, the levels of insulin were increased 5 fold from baseline levels in the territory of SMA. In the patient 5 with negative imaging findings, SACST was performed, but the results were inconclusive due to anatomical variation. Intraoperative USG revealed a tumour in the tail of the pancreas and after enucleation, the tumour was confirmed with pathological examination. Patient 6 with known MEN1 had a tumour in the tail of the pancreas, and SACST showed increased insulin levels in the territory of GDA, SMA, and

**Table 1.** The baseline characteristics of the cases.

Patient	Age (years)	Gender	Plasma glucose nadir (mg/dL)	Insulin (μU/mL)	C-peptide (ng/mL)	Diagnosis	MEN
1	37	Female	42	26.6	6.13	NIPHS	-
2	30	Female	41	11	2.5	NIPHS	-
3	36	Female	27	5.5	1.5	Insulinoma	-
4	21	Female	45	18	14.4	Insulinoma	+
5	28	Male	32	6.3	1.3	Insulinoma	-
6	48	Female	22	8.4	2.35	Insulinoma	+
7	22	Male	34	3.9	0.9	NIPHS	-
8	55	Male	44	600	7	Autoimmune	-

NIPHS: Noninsulinoma pancreatogenous hypoglycemia syndrome, MEN: Multiple endocrine neoplasia.

**Table 2.** Non-invasive imaging methods, selective arterial calcium stimulation test, perioperative findings, surgery data, diagnosis and treatment of the patients.

Patient	Imaging modalities used before SACST						SACST	Intraoperative USG	Treatment	Surgery data (Localization/ size)	Pathologically proven diagnosis	Definite diagnosis	Concordance SACST/Surgery-proven pathology
	USG	CT	MRI	EUS	Somatostatin receptor sintigraphy	DOTATOC							
1	-	No finding	No finding	-	-	-	SMA	Diffuse hyperplasia	Subtotal pan-createctomy	-	NIPHS	NIPHS	No
2	-	-	-	-	-	-	SMA, GDA, SPA	-	Medical treatment	-	-	NIPHS	-
3	No finding	No finding	No finding	-	-	-	SPA	Head/ 14 mm	Whipple operation	Head/14 mm	Insulinoma	Insulinoma	Yes
4	-	No finding	Tumour/ head/ 24 mm	-	No finding	-	SMA	-	Enucleation	Head/24 mm Tail/10 mm	Insulinoma	Insulinoma/MEN1	Yes
5	No finding	No finding	No finding	-	-	-	Not conclusive	Tail/10 mm	Enucleation	Tail/10 mm	Insulinoma	Insulinoma	No
6	-	-	-	No finding	-	Tail	SMA, GDA, SPA	-	Distal pancreatectomy	Tail/55 mm	Insulinoma	Insulinoma/MEN1	No
7	-	-	-	-	-	-	SMA, GDA, SPA	-	Medical treatment	-	-	NIPHS	-
8	No finding	No finding	No finding	-	-	-	SMA, GDA, SPA	-	Medical treatment	-	-	Autoimmune hypoglycemia	-

USG: Ultrasonography, CT: Computed Tomography, NIPHS: Noninsulinoma pancreatogenous hypoglycemia syndrome, MRI: Magnetic Resonance Imaging, EUS: Endoscopic Ultrasonography, DOTATOC: 68Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N',N''-tetraacetic acid-D-Phe1-Tyr3-octreotide, SACST: Selective Arterial Calcium Stimulation Test, SMA: Superior mesenteric artery, GDA: Gastroduodenal artery, SPA: Splenic artery.

SPA. Due to the history of MEN1, discordant SACST findings and the purpose of searching for micrometastasis, DOTATOC was performed, and the tail tumor was seen in the DOTATOC imaging. Distal pancreatectomy confirmed the diagnosis of insulinoma. In patient 8 with negative imaging methods, SACST was performed, and insulin levels increased in the territory of GDA, SMA, and

SPA. The insulin antibodies which resulted too late after SACST were positive in the patient, so autoimmune hypoglycemia was considered as a diagnosis. After corticosteroid treatment, hypoglycemia was resolved (Table 2).

Adverse events such as hypoglycemia or hypercalcemia were not seen during SACST, but in patient 5, the re-

sults were inconclusive due to anatomical variation. Five patients underwent surgery for hypoglycemia after examination with SACST. Enucleation was performed in 2 patients, Whipple operation in 1 patient, subtotal pancreatectomy in 1 patient, and distal pancreatectomy in 1 patient with the diagnosis of insulinoma. Four patients were diagnosed with insulinoma and 1 patient with NIPHS after examination of surgery-resected material. Insulinomas were mostly localized in the tail (75%) with a median diameter of 20.5 (10-55) mm.

A total of five patients who underwent surgery with the diagnosis of insulinoma or NIPHS were assessed with the surgically-taken material. While concordance between SACST and surgery-proven pathology for insulinoma was 50% (2/4), the accuracy in the localization of insulinoma was 25% (1/4).

## Discussion

Hyperinsulinemic hypoglycemia is uncommon. The cause of this clinical problem can be distinguished after using variable biochemical measurements and imaging methods. After oral hypoglycemia agent-induced hypoglycemia was ruled out, insulinoma, NIPHS, and insulin autoimmune hypoglycemia should be thought of as a diagnosis [12]. Insulin autoimmune hypoglycemia occurs in patients who have antibodies directed to endogenous insulin or the insulin receptor. Since in our medical center the antibody testing takes a long time and patient 8 experienced severe hypoglycemia symptoms, he was performed SACST after some negative imaging techniques.

Surgery is the first option for the treatment of insulinoma, and for a more effective surgery, localization of the tumour is important preoperatively [9]. After excluding oral hypoglycemia agent-induced hypoglycemia and insulin autoimmune hypoglycemia, some localization studies should be done to distinguish between the presences of an insulinoma versus NIPHS [13]. Many non-invasive imaging techniques such as CT, MRI, USG, somatostatin analogue-related imaging methods, and PET are important tools in differentiating insulinoma or NIPHS. In our study, 6 patients with negative imaging were performed SACST. Although insulinomas are pancreatic neuroendocrine tumours that are typically solitary, MEN-1-associated insulinomas tend to be multifocal. Due to this tendency, 2 patients with known MEN were performed SACST [14]. Selective Arterial Calcium Stimulation Test is a minimally invasive and effective method for insulinoma localization, and the accuracy of SACST has been shown to range from 94% to 100% [11]. While Morganstein et al. demonstrated that SACST showed 100% accuracy with respect to surgery-proven pathology, we found that concordance between SACST and surgery-proven pathology for insulinoma was 50% (2/4) [15]. Furthermore, the accuracy in the localization of insulinoma was 25% (1/4) in our study. This low rate may be explained by variant pancreatic arterial anatomy. Also in SACST, calcium evokes a characteristic response of discharge of vesicles from tumour cells with a dominant arterial supply. In patients with NIPHS, positive responses are seen after injection of calcium gluconate into multiple arteries, in patients with insulinoma, the response is positive in one artery. If the tumor resides

in an area fed by two arteries, or the patient has multiple insulinomas, the diagnosis may be challenging [12]. In our report, 2 patients with a diagnosis of NIPHS had positive responses after injection of calcium gluconate into multiple arteries, and 1 patient with NIPHS had a positive response in the region of one artery. As a result, in differentiating insulinoma and NIPHS, SACST can be inconclusive. A few patients also may have aberrant arterial anatomy that causes nonsense results. In our study, one patient had an anatomic variation recognized by the interventional radiologist performing the procedure, and the lesion was realized by intraoperative USG.

There are some limitations of the study. Firstly, this report shows single-center experience, and the sample size is small. Secondly, our hospital is a tertiary health center, so patients with negative/doubtful localization findings at other hospitals are usually transferred to our hospital. This might lead to selection bias in this study.

SACST seems to contribute important diagnostic information in the differential diagnosis of hyperinsulinemic hypoglycemia in patients. Although this technique did not have high concordance with surgery-proven pathology and accuracy in the localization of insulinoma, it can have a key role in the differential diagnosis, especially in centers where other imaging techniques are not available, or in cases where other imaging methods obtain suspicious or inadequate diagnosis.

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