



## Determination of the Localization by Intra-arterial Calcium Stimulation in Insulinoma: A Case Report

Mehtap Evran<sup>1\*</sup>, Murat Sert<sup>1</sup>, Tamer Tetiker<sup>1</sup>, Erol Aksungur<sup>2</sup> and Ömer Alabaz<sup>3</sup>

<sup>1</sup>Department of Internal Medicine, Cukurova University Medical Faculty, Division of Endocrinology, 01330 Adana, Turkey.

<sup>2</sup>Department of Radiology, Cukurova University Medical Faculty, 01330 Adana, Turkey.

<sup>3</sup>Department of General Surgery, Cukurova University Medical Faculty, 01330 Adana, Turkey.

### Authors' contributions

Authors ME, MS and TT followed and treated of the patient; author ME managed and researched the literature; author EA performed the hepatic venous sampling with selective intra-arterial calcium stimulation of the patient, author ÖA performed the surgical operation of the patient and authors ME, MS and TT wrote the paper. All authors read and approved the final manuscript.

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Case Study

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### ABSTRACT

**Aims:** Insulinoma, though a very rare disease, is the most common endocrine tumors of the pancreas. High serum insulin levels during hypoglycemic episodes are specific for the diagnosis. Where ultrasonography, tomography and other imaging modalities are not adequate for determination of the adenoma and its localization, hepatic venous sampling method with selective intra-arterial calcium stimulation becomes important in terms of determination of preoperative localization of adenoma and shortening surgery time.

**Presentation of Case:** A 38-year-old female patient investigated for weakness and low blood glucose was examined with a prediagnosis of insulinoma. Although clinical and laboratory results suggested insulinoma, no focus could be found by routine imaging methods. Hepatic venous sampling with selective intra-arterial calcium stimulation of the patient, who had pancreatic angiography, was performed. As a result of calcium stimulation performed from proximal splenic, mid splenic and gastroduodenal arteries, insulin and C-peptide levels in blood samples collected from hepatic vein were found to be high. The patient underwent an operation with intraoperative

\*Corresponding author: Email: [mehtap.evran@hotmail.com](mailto:mehtap.evran@hotmail.com);

ultrasonography in which mass excision of the pancreas tail was performed. Pathologic examination revealed a neuroendocrine tumor showing synaptophysin, chromogranin and NSE (+) staining.

**Discussion and Conclusion:** Hepatic venous sampling with selective intra-arterial calcium stimulation in insulinomas is an extremely accurate and reliable method for the preoperative localization.

*Keywords: Hypoglycemia; insulinoma; localization; calcium stimulation test.*

## 1. INTRODUCTION

Pancreatic insulinoma is a rare neuroendocrine tumor and its prevalence is 4 million cases /year [1]. The majority of patients diagnosed with insulinoma are between 30 and 60 years of age, and 59% of them are female [2]. Patients usually present with hypoglycemia, and high insulin levels measured during hypoglycemia attack are considered as a diagnosis for insulinoma [3,4]. The number of patients diagnosed has increased with advances in imaging techniques and their frequent use. Surgical removal of the tumor is the first choice in treatment, and chance of cure is high [5,6]. Insulinomas are benign tumors mostly smaller than 2 cm, however, they may cause fatal hypoglycemia risk [7]. Therefore, their early diagnosis and preoperative localization are very important. This paper aims to present a case for whom we determined preoperative adenoma localization by selective intra-arterial calcium stimulation and whom we cured with surgery.

## 2. PRESENTATION OF CASE

A 38-year-old female patient was hospitalized with a pre-diagnosis of insulinoma. It was learned from patient's history that she was hospitalized in another university hospital 1 year ago due to inability to talk and walk early in the morning. During her follow-up, her plasma glucose values were 25-41-32 mg/dl and her insulin and C-peptide levels measured at the time of hypoglycemia were high so her tests for insulinoma were scheduled. In abdominal computed tomography (CT) performed on 09/2012, diffuse thickening of the gastric antral wall and diffuse wall thickening involving almost the entire left hemicolon were detected. In upper gastrointestinal system (GIS) endoscopy performed on 12/2012, slack in lower esophageal sphincter, gastritis and fundic polyps were detected, however, colonoscopic examination was normal. It was learned that the patient was prescribed prednisolone and serotonin reuptake inhibitor upon diagnosis of adrenal insufficiency, and then discharged, however, even though she

used these medications, she became unconscious and had hypoglycemia attack 2 more times at home during a period of 2 months. It was learned that her control tests were performed in the same hospital and prednisolone treatment was discontinued, and that on 7/2013, she had an abdominal magnetic resonance imaging (MRI) scan, octreotide scintigraphy and abdominal aorta, celiac, superior mesenteric artery angiography upon persisting complaints in the last 8 months, and the results of such procedures were found to be normal.

In patient's history, there wasn't any illness, operation or prescribed drugs other than those mentioned above. She had no history of smoking or alcohol use.

According to her family history, her mother had hypertension and breast cancer, and her father had hypertension.

The patient's data according to her physical examination were as follows: height: 165 cm, weight: 90 kg, body mass index (BMI): 33 kg/m<sup>2</sup>, arterial blood pressure: 110/70 mmHg, pulse: 82 /min, rhythmic. Her general state was good; she was conscious and cooperative and no pathology was found during examination of her organ systems.

The results of her laboratory tests performed upon her hospitalization were as follows were found normal, but, blood glucose level was 25 mg/dl. Her EKG was consistent with sinus tachycardia.

She was admitted to our clinic and her blood glucose was monitored. During her follow-up, hypoglycemia (blood glucose: 25-32-70-62-50-28 mg/dl) was observed, and according to the tests conducted at the time of hypoglycemia, C-peptide > 40 ng/ml, and insulin > 305 µ/ml. Expected insulin/glucose ratio was ≥0.3, however, that ratio was 9.5 in the patient and insulinoma was considered. In addition to the patient's previous imaging tests,

endosonography was performed on the patient and no mass suggesting insulinoma was detected. Therefore, it was planned to perform hepatic venous sampling with intra-arterial calcium stimulation. The patient did not have any contra-indication that may interfere with intra-arterial calcium stimulation. Informed consent form was taken from the patient.

### 3. CALCIUM STIMULATION TEST PROCEDURE

On 23.08.2013, during angiography performed by entering from right common femoral artery and left common femoral vein following local anesthesia, superior mesenteric artery (SMA), A.Hepatica propria, splenic artery proximal and middle parts and gastroduodenal artery (GDA) were selectively catheterized. An interval of minimum 5 minutes was allowed between arterial catheterizations. 5 ml bolus Ca-gluconate (0.024 mEq/kg) was diluted with saline and given to the catheterized artery with a fast injection. Then, blood samples of 5 ml were taken from hepatic vein at 0, 30, 60 and 120 seconds for insulin and C-peptide. The patient's vital signs were monitored throughout the test. No hypoglycemia attack was observed during the process. The results are shown in Table 1.

In samples collected from hepatic vein at 30 or 60 seconds (or at both times), a 2-fold increase in insulin levels as compared to those before prestimulation is considered as a positive finding. Accordingly, in GDA or SMA samples, a 2-fold increase in insulin levels as compared to those before prestimulation indicates pancreatic head or uncinate localization, while any increase in proximal splenic artery samples indicates corpus or caudal localization [8]. As a result, it was thought that our patient may have a tumor at head or tail of pancreas, which is fed by proximal splenic, mid splenic arteries and gastroduodenal artery. However, increase in C-peptide levels in proximal splenic artery samples was higher than in GDA samples. The patient underwent an operation with intra-operative ultrasonography (US) and a mass measuring 1.5x1x0.5 cm was excised in the pancreatic tail. As a result of pathological examination of the mass, it was reported that "neuroendocrine tumor, pancreatic, frozen samples, biopsy; synaptophysin, chromogranin and NSE applied by immunohistochemical method revealed staining in tumor cells (+). Proliferation index with Ki67 was determined as 1-2%". In the postoperative period, the patient's blood glucose was 92 mg/dl, insulin 5 µU/ml, and C-peptide 2 ng/ml. The patient is in her post-operative 2nd year and monitored as healthy.

**Table 1. The results of hepatic venous sampling with preoperative selective intra-arterial calcium stimulation** <sup>(a, b, c)</sup>

Artery	Time (second)			
	0.	30.	60.	120.
<b>Proximal splenic</b>				
Insulin	>305	>305	>305	>305
C-peptide	>40	37.7	>40	>40
<b>Mid splenic</b>				
Insulin	56	286	>305	>305
C-peptide	9.4	>40	>40	>40
<b>Hepatica propria</b>				
Insulin	55.6	51	46.8	52
C-peptide	9.1	9	8.7	9
<b>Superior mesenteric</b>				
Insulin	48.2	40	41.2	40
C-peptide	8.2	7.9	8	7.9
<b>Gastroduodenal</b>				
Insulin	268	256	>305	246.8
C-peptide	22.3	28	28.4	22

<sup>a</sup>Normal range of insulin: 1.9-23 µU/ml

<sup>b</sup>Insulin (IU/ml)/(glucose (mg/dl) ratio 0.3≥ pathologic,

<sup>c</sup>Normal range of C-peptide :0.9-4.3 ng/ml

#### 4. DISCUSSION

Diagnosis of insulinoma should be considered for patients presenting with hypoglycemia symptoms, referred to as conventional Whipple triad [9]. In patients thought to have insulinoma, insulin and C-peptide levels can be measured at the time of hypoglycemia by carrying out a 72 h- delayed fasting test. In the presence of insulinoma, hypoglycemia is usually expected to take place within the first 24 h of fasting test [10]. Knowing localization of insulinoma is important in terms of determination of localization of surgical procedure and preventing performance of a blind pancreatectomy [11]. Several methods, including abdominal US, CT, MRG, angiography, somatostatin receptor scintigraphy, endosonography and intraoperative US, can be used to determine localization [12]. However, in the presence of adenoma and where it is not possible to determine its localization, it is possible to make a diagnosis by hepatic venous sampling with selective intra-arterial calcium stimulation [7,13].

The procedure was applied for the first time by Doppman et al. [8,14] in 1991 and 1993, and they correctly localized the tumor in 56% of the patients in which they measured insulin secretions by performing selective intra-arterial calcium stimulation. In many subsequent studies, insulin secretion was investigated by selective intra-arterial calcium stimulation method and this method has been thought to be a powerful method to determine tumor localization [15,16]. However, Sung et al. study, in which the authors performed hepatic venous sampling with selective intra-arterial calcium stimulation and monitored 8 patients, reported that measuring only insulin gradient had a sensitivity of 86% and measuring C- peptide gradient in addition to insulin had a sensitivity of 100% in determination of tumor localization [17]. In a case report presented by General et al., insulin and C-peptide measurements were made together and it was emphasized that utilization of hepatic venous sampling with selective intra-arterial calcium stimulation in conjunction with intra-operative US is important for determination of localization and the success of surgery [2]. In a retrospective study on patients diagnosed with insulinoma in the US between 1996 and 2008, tumor localization was correctly determined in 38 of 45 patients on whom hepatic venous sampling with selective intra-arterial calcium stimulation was performed, however, a false-positive localization was determined in 2 patients and a

false-negative localization was determined in 2 patients. In this study, localization sensitivity was found to be similar in head/neck and tail lesions of pancreas (82% and 88%, respectively) [18]. During hepatic venous sampling with selective intra-arterial calcium stimulation conducted on our patient, her insulin and C-peptide levels were measured together, and she was thought to have a tumor in head or neck section of pancreas. Furthermore, increase in C-peptide levels in proximal splenic artery samples was higher than in GDA samples. These findings would suggest that the presence of a mass in pancreatic tail, and tumor excision was performed on tail section of pancreas during the surgical intervention by intra-operative US.

Tumoral structures were also shown in patients by other imaging methods in general in other studies. In the case of our patient, despite hypoglycemia symptoms lasting for 1 year and high insulin and C-peptide levels measured at the time of hypoglycemia attack, no tumoral structure was detected in pancreas by imaging methods in other university hospital, and a diagnosis was achieved by performing selective intra-arterial calcium stimulation.

#### 5. CONCLUSION

In conclusion, where the patient is thought to have insulinoma and it's not possible to make a diagnosis by other imaging methods, performance of hepatic venous sampling with selective intra-arterial calcium stimulation is an important choice in terms of determination of the presence and localization of tumor preoperatively as well as shortening surgery time.

#### CONCENT

Informed consent form was taken from the patient.

#### ETHICAL APPROVAL

It is not applicable.

#### COMPETING INTERESTS

Authors have declared that no competing interests exist.

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