Preoperative Endoscopic Ultrasound (EUS) Imaging in Diagnosis of Insulinomas in a University Hospital in Damascus

¹Hazem B. Aljasem & ^{2*}Zaynab. Alourfi

¹Faculty of Medicine, Department of Surgery, Damascus University, Damascus, Syria.

²Faculty of Medicine, Department of Internal Medicine. Damascus University, Damascus, Syria.

***Corresponding Author:** Zaynab. Alourfi, Faculty of Medicine, Department of surgery, Damascus University, Damascus, Syria.

Email: zaynabarfi@hotmail.com, **Tel:** 00963955380236

Citation: Zaynab. Alourfi et al. Preoperative Endoscopic Ultrasound (EUS) Imaging in Diagnosis of Insulinomas in a University Hospital in Damascus. Int J clinical & case studies. 1:1, 17-21

Copyright: © 2017, Zaynab. Alourfi et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Received January 12, 2017; **Accepted** January 15, 2017; **Published** January 28, 2017.

Abstract

Introduction: Endoscopic ultrasound (EUS) is a very important procedure to preoperatively localize insulinomas and plan the surgery. This end with less time and less invasive surgical approach. However, under optimal conditions, about 10-20% of insulinomas are missed even by experts. The purpose of this retrospective study was to recognize factors that could affect EUS results.

Methods: This study was carried out at Al-Assad University Hospital (AUH), Damascus, Syria. Eighteen patients fulfilled the inclusion criteria (positive 72 hours fasting test and successful surgery with histopathology confirmation). All EUSs were performed by one experienced examiner.

Results: All 18 cases were benign insulinomas (16 were tumors and two were hyperplasias). Preoperative EUS did not detect six tumors (negative EUS). They were all isoechoic to surrounding normal pancreatic tissue. The ten detected cases (positive EUS = 62.5%) were hypoechoic, isoechoic or hyperechoic lesions. Positive EUS patients were younger than negative EUS patients ($P=0.05$). The mean tumor diameter in positive EUS was significantly larger than negative EUS ($P=0.04$).

Conclusion: Some Isoechoic Insulinomas were not detected by EUS imaging. Smaller tumor diameter and older age of the patient might be behind negative imaging.

Keywords: Preoperative Diagnosis, Insulinoma, Endoscopic Ultrasound, EUS

Introduction

Insulinomas are endocrine pancreatic beta cells tumors. Even though they are rare, insulinomas are the most common functioning islet cell tumor of the pancreas. Their incidence is about one in 250,000 patient/year (Cryer, 2008; Hoem, 2008). Patients are almost always cured lifelong with complete elimination of a benign insulinoma (Grant, 2005). Mehrabi et al, in 2014, carried out a systematic review for 114 articles with 6222 cases of insulinoma. They reported that patients with insulinomas are mostly in their fifties, with a higher incidence in men. In conclusion they found that insulinomas are mostly sporadic (94%), benign (87%), and single (90%) (Mehrabi A, et al. 2014). About 10% of insulinoms are part of Multiple endocrine neoplasia type 1 (MEN-1) (Thakker RV, et al, 2012; Carroll RW, 2013). In-

hospital watched full prolonged (72h) fasting test is the confirming diagnostic test of insulinoma with an accuracy of approximately 100% (Kann PH, et al, 2007). After that, it is mandatory to localize insulinoma by imaging procedures. These are non-invasive such as abdominal sonography, magnetic resonance imaging (MRI), computed tomography (CT), and the scintigraphy of somatostatin receptors. Other procedures are invasive such as preoperative and intra-operative endoscopic ultrasound (EUS). However, all these methods have low sensitivities (Müller et al, 1994; Zimmer T, et al, 2000; Kann P & Zielke A, 2005; Kaczirek K, et al, 2004).

The intra-operative EUS is more accurate and could improve the detection of pancreatic tumor (near 100%) (Chung JC, et al, 2006). Since 1990s EUS has been considered the reference method in

localizing insulinomas with using a high-frequency sonography probe, that can get very close to the pancreas (Kann P 2016, McLean, A. M. and Fairclough P. D, 2005; Nesje LB, et al, 2002). Preoperative EUS helps in surgical planning to end with minimal invasive approach in shorter time. This because it precisely localize the tumor and its relation to vital structures (vessels, bile and pancreatic duct), in addition to determine whether the disease is uni- or multifocal (Fendrich V, et al, 2004; Langer P, et al, 2005; Kann P, et al, 2001; Kann P, 2006). It could also distinguish benign from malignant lesions and confirm that by guided fine needle aspiration (Gornals J, et al 2011; Leelasinjaroen P et al, 2014).

EUS detection rates ranged between 86.6% and 93% (Okabayashi T, et al, 2013; Tavcar I, et al, 2014). In 2015, Tellez-Avila et al reported that EUS sensitivity, positive predictive value, and accuracy are 100 %, 95.4 %, 95.4 % respectively. Despite this, 10-20% of insulinomas cannot be diagnosed by EUS, even with experienced examiners and under optimal conditions (Tellez-Avila et al 2015 , Kann P & Zielke A, 2005; Mirallie E, et al, 2002). Above and beyond examiner's experience, many factors that might affect EUS outcome were reported . First, different devices have different accuracies (i.e. higher frequency in MHz gives higher accuracy) (Bhutani, Deutsch, 2010). Second, EUS should be done under standardized conditions (like sedation and positions of the patient). Finally, there might be factors that are related to patients; Kann et al, reported that low body mass index, female gender, and young age are associated with negative EUS (Kann P, et al, 2007).

The purpose of this study was to recognize factors that might affect EUS imaging in patients with pancreatic insulinomas. This could help in finding new ways or techniques to avoid false negative results. There is no such study in Syria.

Materials and Methods

This retrospective study was carried out at Al-Assad University Hospital (AUH) in Damascus, Syria. Inclusion criteria were: a positive 72 hour fasting test, preoperative EUS imaging, successful surgery and histopathology.

72h fasting test protocol in AUH: No food intake but patient is allowed to drink calorie-free and caffeine-free beverages. Blood specimens are collected for measurement of blood glucose every six hours until the glucose concentration is below 60 mg/dL (3.3 mmol/L); at this point, the frequency of sampling is increased to once every one to two hours. The test is ended when blood glucose concentration is ≤ 45 mg/dL (2.5 mmol/L), the patient has symptoms or signs of hypoglycemia, or when the blood glucose concentration is less than 55 mg/dL (3 mmol/L) if Whipple's triad (hypoglycemic symptoms that improved with eating) was documented on a prior occasion. Blood specimen is collected before allowing the patient to eat for blood glucose, insulin, C-peptide, and cortisol (to rule out adrenal insufficiency)

72h fasting test is positive when insulin-glucose ratio is > 0.25 (Wiesli P, et al, 2002). Exploratory surgery may be established after positive 72h fasting test even if all of the other diagnostic procedures were negative.

All EUSs were done by the same expert examiner using the same device, OLYMPUS EndoEcho (EU-C 2000 endosonoscope) with OLYMPUS UWS-1 water supply unit (for ultrasonic endoscope), and OLYMPUS OEV181H high definition monitor.

The patients were positioned in the left decubitus and under conscious sedation. Fiberscope is inserted as far as the second portion of the duodenum in oblique-viewing with the transducer located at the tip of the fibroscope. Scanning was performed with de-aerated water filled balloon applied to the tip of the echoendoscope. Primarily, pancreatic head was scanned for exploration of the entire head of the pancreas, the instrument was straightened in the same way as endoscopic retrograde cholangiopancreatography (ERCP). The probe was adherent to the duodenal wall. If the insertion depth of the instrument was correct, the pancreatic head and the uncinate process could be seen. Then, the endoscope was drawn backwards to the stomach and scanning of the rest of the pancreas was performed. The pancreas was scanned longitudinally in a craniocaudal direction with clockwise rotation and slight retraction of the scope towards the spleen then the pancreatic body and tail were imaged (Dietrich, 2006).

The following information were extracted from patients records, EUS, surgical and histopathology reports: gender (female/male), age, body mass index BMI (kg/m²) (four were missing), largest tumor diameter (mm, taken from preoperative EUS imaging, and from the report of histopathology if EUS negative) (one was missing), the histopathology of tumor (benignancy/malignancy), fasting test, highest ratio: insulin serum concentration (μ U/ml)/ blood glucose (mg/dl) (during hypoglycemia in the 72h), and echogenicity of tumor (hypo-/iso-/hyperechoic).

SPSS 18 software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis. Nonparametric tests (Mann-Whitney Test for continuous variables) were used because of the small sample size (non-normal distribution). Chi-square test was used for categorical variables. Statistical significance level: $P \leq 0.05$ was considered significant. Results were reported as means and standard deviation (SD).

RESULTS

130 records with different causes of hypoglycemia between 2006 and 2012 were systematically reviewed. 20 patients of them (15%) were diagnosed with insulinomas. However, 18 of them fulfilled the inclusion criteria. Two were pancreatic hyperplasia (11%) and 16 were tumors (five males and 11 females) (Table 1). Hyperplastic lesions were excluded as they cannot be discovered by EUS (false negative imaging)

Of the 16 subjects, 10 (62.5%) were EUS positive, 6 (37.5%) were EUS negative (Fig. 1). EUS positive and EUS negative groups were similar in respect to gender (70% female vs. 67% female, respectively). The EUS positive group was found to be younger in age than the EUS negative group (25.0 ± 11.7 years vs. 37.8 ± 11.6 years, respectively; $p = 0.05$). The EUS negative group had a smaller mean tumor diameter than the EUS positive group (9.4 ± 3.8 mm vs. 15.2 ± 5.3 mm, respectively; $P=0.04$). There was no

Table (1) Patient's data, EUS findings, and tumor characteristics

Number	Gender	Age(years)	BMI (kg/m ²)	Tumor diameter(mm)	Insulin (μU/ml)	*Insulin-glucose ratio (μU/ml per mg/dl)	Histology	Detection	Location
1	M	35	24.2	10	18.9	0.32	B	N	Body
2	M	41	NA	6	35.5	1.18	B	Y	Body
3	F	23	30.7	24	56.78	1.27	B	Y	Body
4	F	30	NA	7	15.2	0.4	B	N	Tail
5	F	13	26.33	20	98.55	2.46	B	Y	Body
6	F	20	27.12	15	22.08	0.49	B	Y	Head
7	F	27	25.71	13	10.8	0.35	B	Y	Body
8	F	11	22.48	15	22.07	0.55	B	Y	Neck
9	M	46	NA	19	688.5	12.5	B	Y	Body
10	M	19	NA	20	5.92	0.065	B	Y	Tail
11	F	44	23	5	47	1.46	B	N	Body
12	M	58	40.74	15	30.93	0.65	B	N	Tail
13	F	17	28	12	24	0.68	B	Y	Body
14	F	33	23.43	18	52.15	1.1	B	Y	Body
15	F	26	28.5	NA	23.7	1.03	B	N	Head
16	F	34	22.5	10	26.4	0.48	B	N	Body

M= male, F=female, Y=yes, N=no, NA: not available. B= benign

* insulin and insulin-glucose ratio were taken during episodes of hypoglycemia in the prolonged fasting test.

significant difference observed between EUS positive and negative groups when it came to insulin-glucose ratio (2.06 μU/ml per mg/dl vs. 0.72 μU/ml per mg/dl, respectively) or BMI (26.3 kg/m² ± 2.8 kg/m² vs. 27.8 ±10.2 kg/m², respectively) (Table 2).

Binary logistic regression (detection as dependent, age and tumor size as covariates) reveals no significance.

DISCUSSION

Our study showed that smaller tumor diameter and older age of patient might affect EUS detection ability and end with negative result. It is reasonable that the larger the tumor diameter the higher

the chance of detection. The echogenicity of the pancreas increases with age beginning at the 4th decade of life which means that the pancreas echogenicity is higher than the liver's (Glaser J, et al, 2000). Increasing age or obesity leads to a uniform increase in echogenicity that is referred to as pancreatic lipomatosis this greatly increase the contrast to anechoic splenic vein and the confluence of the portal vein. Pancreatic tumors are often more hypoechoic than the rest of the parenchyma and are difficult to be distinguish from adjacent bowel loops or peripancreatic lymph nodes. This might explain the tendency to have negative EUS in older patients.

Table (2) EUS positive group Vs EUS negative group characteristics

Comparing items	EUS positive group	EUS negative group	P
Sex	3 males and 7 females	2 males and 4 females	1
Age	(25 ± 11.7 years)	(37.83 ± 11.56 years)	0.05
The mean tumor diameter	(15.20 ± 5.26 mm)	(9.40 ± 3.78 mm)	0.04
The mean insulin-glucose ratio	(2.06 µU/ml per mg/dl)	(0.72 µU/ml per mg/dl)	0.40
BMI	(26.25 kg/m ² ± 2.77 kg/m ²)	(27.78 ± 10.24 kg/m ²)	0.93

EUS: endoscopic ultrasound. BMI: body mass index.

Our results did not match with Kann et al results which reported that low body mass index, female gender, and young age all associated with negative EUS. These differences between our study and theirs might be explained by three reasons. First, they have a larger sample size than ours (29 patients vs. 16). Second, different devices and examiners might end with different results. Finally, while our patients were lying on the left side, their patients were in supine position. The former position of patient might give negative EUS, because the transducer of the fibroscope might go to a more lateral position by sliding over the pancreas. Some studies reported that repeating EUS with a supine position might make negative EUS positive. Because small sample size is the main limitation,

further studies are warranted to be carried out with a larger sample size. Being a retrospective study is another limitation. Prospective study considering these risk factors (which we concluded) and changing position to the supine one in case EUS with left position is negative, might end with different results.

Acknowledgment: The authors wish to thank Faculty of Medicine, Damascus University and AUH for ethical approval. They also thank Dr. Muhammad Rafat B. Meda and Dr. Mohamad Emad S. Abdulrhman for assistance in data collecting. They appreciate

Miss HEND Alkabbani, and all members of medical record department at AUH for their help.

Figure.1.EUS images. A: Normal pancreas. B: Isoechoic insulinoma (white arrow) and C: Hypoechoic insulinoma (white arrow).

REFERENCES

1. Carroll RW. 2013. Multiple endocrine neoplasia type 1 (MEN1). *Asia Pac J Clin Oncol*. Dec;9(4):297-309.
2. Chung JC, et al, 2006. Localization and surgical treatment of the pancreatic insulinomas *ANZ J Surg*. Dec;76(12):1051-5.
3. Cryer, P. E, 2008. Glucose homeostasis and hypoglycemia, in *Williams Textbook of Endocrinology* (11th edition) ;1503-1533.
4. Dietrich, 2006. Longitudinal EUS anatomy. *Endoscopic Ultrasound: An introductory Manual and Atlas* 2nd edition.;11-14.
5. Fendrich V, et al, 2004. Diagnosis and surgical treatment of insulinoma - experiences in 40 cases. *Deutsche Medizinische Wochenschrift*.;129 941 - 946.
6. Glaser J, et al, 2000. pancreas and aging: a study using ultrasonography. *Gerontology*. Mar-Apr.;46(2) 93-6.
7. Gornals J, et al, 2011. Definitive diagnosis of neuroendocrine tumors using fine-needle aspiration-puncture guided by endoscopic ultrasonography. *Rev Esp Enferm Dig*; 103: 123-128.
8. Grant CS. 2005. Isulinoma. *Best Pract Res Clin Gastroenterol*.;19 (5): 783-98. Hoem D, et al 2008. A clinicopathological characteristics and non-adhesive organ culture of insulinomas. *Scand J Surg*. 97(1):42-9.
9. Kaczirek K, et al, 2004. The importance of preoperative localisation procedures in organic hyperinsulinism--experience in 67 patients. *Wien Klin Wochenschr*. Jun 30;116(11-12):373-8.
10. Kann P, et al, 2001. Endosonography of insulin-secreting and clinically non-functioning neuroendocrine tumors of the pancreas: criteria for benignancy and malignancy. *European Journal of Medical Research*.;6 385-390.
11. Kann PH & Zielke A, 2005. Endoscopic ultrasound imaging of insulinoma: limitations and clinical relevance. *Experimental and Clinical Endocrinology and Diabetes*.;113 471-474.
12. Kann PH, 2006. Endoscopic ultrasound imaging in neuroendocrine pancreatic tumors. A critical analysis, *Med Klin (Munich)*. Jul 15;101(7):546-51(Abstract)
13. Kann PH, et al, 2007. Preoperative diagnosis of insulinoma: low body mass index, young age, and female gender are associated with negative imaging by endoscopic ultrasound. *Eur J Endocrinol*. Aug;157(2):209-13.
14. Kann P, 2016. Endoscopic Ultrasound in Endocrinology: Imaging of the Adrenals and the Endocrine Pancreas. Buchfelder M, Guaraldi F (eds): *Imaging in Endocrine Disorders*.Front Horm Res. Basel, Karger, 2016, vol 45, pp 46-54
15. Langer P, et al, 2005. Minimal-invasive operative treatment of organic hyperinsulinism. *Deutsche Medizinische Wochenschrift*.;130 514-518. (Abstract)
16. Leelasinjaroen P, et al, 2014. Role of preoperative endoscopic ultrasound-guided fine-needle tattooing of a pancreatic head insulinoma. *World J Gastrointest Endosc*; 6(10): 506-509.
17. Matthias Hofer, 2013. *Ultrasound Teaching Manual: The Basics Of Performing and Interpreting Ultrasound Scans* (3rd edition); pancreas other cases.
18. McLean, A. M. and Fairclough P. D, 2005. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. *Best Practice and Research Clinical Endocrinology and Metabolism*.;19(2): 177-193.
19. Mehrabi A, et al. 2014. A systematic review of localization, surgical treatment options, and outcome of insulinoma *Pancreas*. Jul;43(5):675-86.
20. Mirallie E, et al, 2002. Value of endoscopic ultrasonography and somatostatin Receptor scintigraphy in the preoperative localization of insulinomas and gastrinomas. Experience of 54 cases. *Gastroenterologie Clinique et Biologique*.;26 360-366. (Abstract)
21. Müller MF et al, 1994. Pancreatic tumors: evaluation with endoscopic US, CT, and MR imaging. *Radiology*. Mar;190(3):745-51. (Abstract)
22. Nesje LB, et al, 2002. Endoscopic ultrasonography for preoperative diagnosis and localization of insulinomas. *Scandinavian Journal of Gastroenterology*.;37 732-737.
23. Okabayashi T, et al, 2013. Diagnosis and management of insulinoma. *World J Gastroenterol*. Feb 14;19(6):829-37.
24. Tavcar I, et al, 2014. A 60-year experience in the treatment of pancreatic insulinoma in the Military Medical Academy, Belgrade, Serbia. *Vojnosanit Pregl*. Mar;71(3):293-7.
25. Thakker RV, et al, 2012. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab*. Sep;97(9):2990-3011.
26. Wiesli P, et al, 2002. A plasma glucose concentration below 2.5 mmol/L is not an appropriate criterion to end the 72-h fast. *Journal of Internal Medicine*.;252 504-509.
27. Zimmer T, et al, 2000. Endoscopic ultrasonography of neuroendocrine tumors. *Digestion*.;62 45-50.