Is the Size of Insulinoma Predictive for its Endocrine Behavior? An Endoscopic Ultrasound Study

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ABSTRACT

Objective Insulinoma is a rare tumor of the pancreas that can lead to spontaneous hypoglycemia due to excessive insulin secretion. Seventy-two-hour fast is the gold standard for finding the correct diagnosis. Endoscopic ultrasound *(EUS)* is an established examination method to identify the suspicious lesion. Previous studies correlate the measured size of insulinoma and their endocrine behavior. This study was designed to find a relation between these variables.

Methods We took the data of patients who had a histologically confirmed insulinoma after receiving an endoscopic ultrasound in our department. Size and echogenicity were correlated with the endpoint of the 72-hour fast and hormone levels.

Results A total of 45 patients were identified. Most insulinomas were small with a volume of < 2 cm^3 (median 1.15 cm^3). There was no correlation between the duration of fasting, hormone levels, and the size of the insulinoma. In addition, in a subgroup analysis, no connection could be established between the size of the insulinoma and the amount of insulin released after oral glucose exposure. We found that homogeneous tumors were significantly smaller and had a lower Ki-67 index. Furthermore, there was a tendency towards a shorter duration for the 72-hour fast for the small tumors.

Discussion This data suggests that the measured size of insulinoma by EUS is not related to the time until termination of the 72-hour fast and measured hormone levels. The echogenicity seems more important, showing that homogenous tumors are an indicator of a higher differentiation, which can result in a shorter duration of the fasting period. The differences in the secretion behavior of the insulinomas could complicate the correlation of size and the 72-hour fast period.

Introduction

Insulinoma is a rare tumor of the endocrine pancreas with an incidence of 1–4/100.000 per year [1]. It can cause spontaneous hypoglycemia due to excessive insulin production [2]. Women are more likely to get an insulinoma [3], and there is a peak of manifestation in the 5th decade of life [4]. Mostly, insulinomas are small solitary lesions, that are benign [5]. The 72-hour fast is the gold standard diagnostic test for recreating the conditions that lead to hypoglycemia [6]. Surgical resection is the preferred therapy because of its curative intention [7]. Preoperative precise localization is mandatory but often difficult [8]. The most commonly used techniques for localization include transabdominal ultrasound (*US*), computer tomography (*CT*), and magnetic resonance imaging (*MRI*). All listed modalities are able to detect insulinomas with a sensitivity up to 80 % [9]. Endoscopic ultrasound (*EUS*) is another established method to find the suspicious lesion. Although invasive, it has little to no harm to the patient and is the most sensitive method to localize this pancreatic tumor [10]. Although established diagnostic routes and criteria lead to correct results, there is often a delay in making an accurate diagnosis. Reasons for this are unspecific symptoms, which range from

neuroglycopenic features to autonomic errors [11]. The reason that neuroendocrine tumors are slow-growing neoplasms and liberate insulin and proinsulin in secretory bursts [12] aggravates these pitfalls. Only a few publications have investigated the correlation between the size of the tumor, their characteristics, and the duration of the 72-hour fast [13, 14]. This study aimed to survey whether the measured size by EUS, the echogenic texture, and secretory characteristics of insulinoma correlate with the duration of the fasting test and hence the severity of the disease.

Methods

This retrospective study included 45 patients diagnosed with insulinoma. Each tumor was examined endosonographically by one single investigator *(phk)* in the university hospitals in Mainz and Marburg, Germany. Endosonographic ultrasound was performed with Pentax FG32UA and FG36UX endoscopes (Pentax cooperation, Tokyo, Japan) with a longitudinal 7.5 MHz sector array combined with a Hitachi EUB 420 or Hitachi EUB 525 ultrasound computer (Hitachi medical cooperation, Tokyo, Japan).

The inclusion criteria were:

- Positive 72-hour fast due to biochemical and clinical values [11]
- Cyto-/histopathological confirmed insulinoma
- Available sizes of insulinoma, measured by endoscopic ultrasound and description of morphology by *EUS*
- Available and complete data on insulin, C-peptide, proinsulin, and duration of 72-hour fasting
- No relapse of an insulinoma

With the help of two diameters (longest and the diameter at 90 °) from the *EUS* and the mean calculated value of these, a spherical volume was defined using the following formula:

$V = 1/6 * \pi * d^{3.}$

Insulin and C-peptide were tested by CLIA-Test (chemiluminescence immunoassay, Elecsys Insulin, and Elecsys C-Peptide, Roche Diagnostics GmbH, Mannheim, Germany) and proinsulin by an enzyme-linked immunosorbent assay (ELISA)-test kit (Immundiagnostik AG, Bensheim, Germany).

For the 72-hour fast, we used the absolute time from the beginning until diagnostic criteria for discontinuing were met (▶ **Table 1**), and hormone levels (insulin, C-peptide, and proinsulin) were documented at this endpoint.

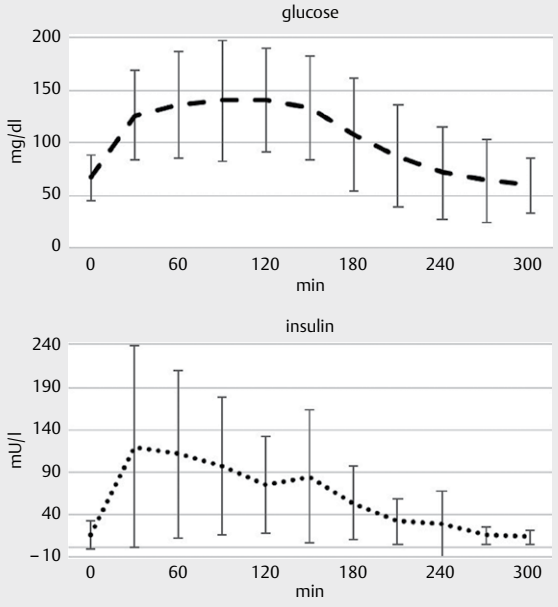
We calculated the area under the curve of insulin (AUCinsulin) by applying the trapezoid rule from a 5-hour oral glucose tolerance test (OGTT) with 75 g of glucose. This data was collected from 16 patients. Furthermore, we plotted and visualized the mean values for insulin and glucose over the time measured (▶ **Fig. 1**).

Statistical analysis was performed with jamovi software (version 1.6.18) and Microsoft Excel for Mac (version 16.29).

We used univariant *linear regression* to determine the association between the duration of the 72-hour fast, insulin, C-peptide, proinsulin levels, and the AUCinsulin (subgroup analysis of 16 patients) and the volume measured by EUS. Due to the non-existent normal distribution of the residuals, we used the bootstrapping method [15]. This analysis was made with the help of SPSS (version 2020 for Mac). We used 2000 samples for *bootstrapping* with a *95 % bias-corrected and accelerated confidence interval*.

▶ **Table 1** The diagnostic criteria for the 72-hour fast for the detection of endogenous hyperinsulinism (adapted from [6, 40]).

Plasma glucose	≤ 45 mg/dL (2.5 mmol/L)
Insulin	≥ 6 µU/mL (≥ 36 pmol/L)
C-peptide	≥ 0.6 µg/L (≥ 2 nmol/L)
Proinsulin	≥ 5 pmol/L
ß-hydroxybutyrate	≤ 2.7 mmol/L
No evidence for exogeneous insulin or insulin secretagogues	



▶ **Fig. 1** The mean curves of insulin and glucose after glucose exposure with 75 g oral glucose with standard deviation.; The mean value curves for insulin and glucose showed a parallel course. However, the insulin values indicate a high standard deviation, assuming a strong heterogeneity of the secretion behavior. Furthermore, 50 % of the patients had hypoglycemia after glucose exposure.

In addition, we recorded specific properties of echotexture by means of EUS, based on the experience and assessment of the examiner (▶ **Fig. 2 a,b**).

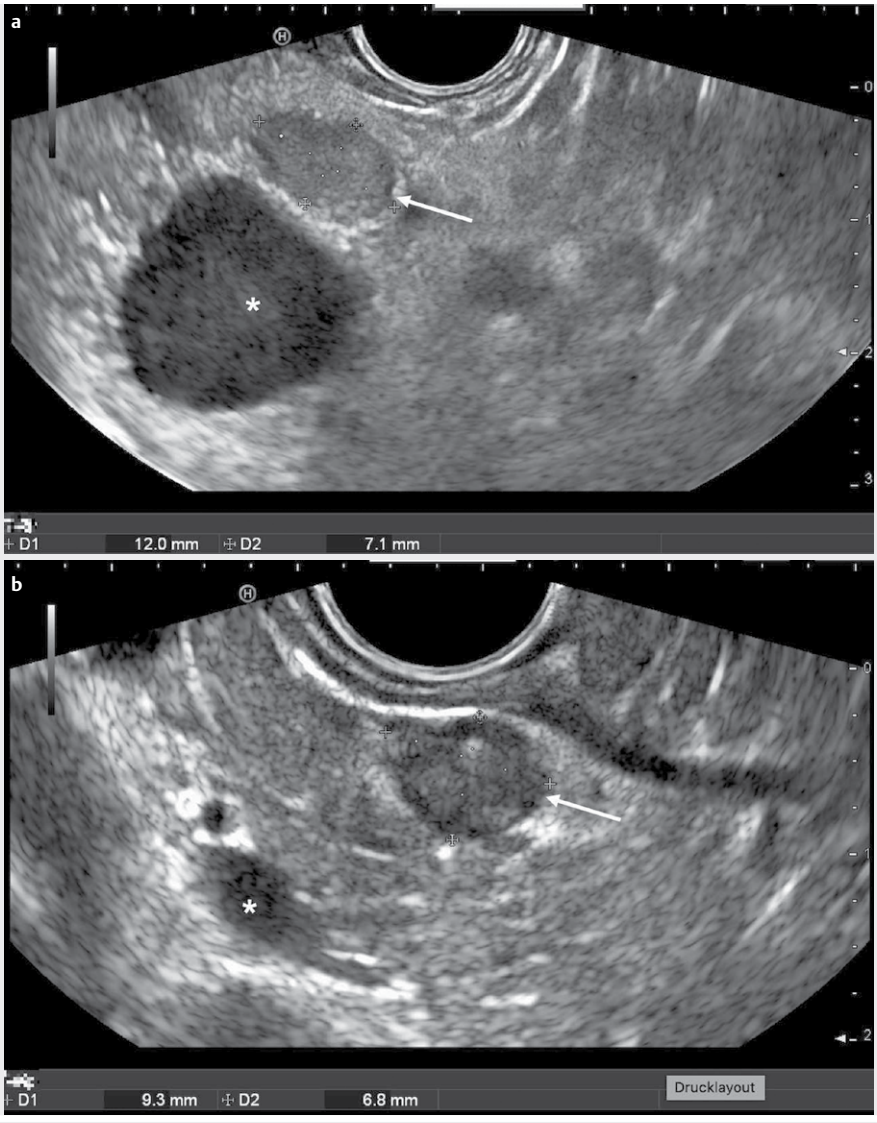
We divided the study population into two groups: homogenous and non-homogenous echogenicity [16].

The differences between homogenous tumors and non-homogenic ones were assessed in terms of their size, duration of the 72-hour fast, Ki-67 index, and hormone levels.

For comparisons between these two, the *Mann-Whitney U test* was used. Statistical significance was assumed at a *P*-value of < 0.05.

Results

We examined 28 females (62.2 %) and 17 males (37.8 %), with a mean age at the time of diagnosis of 47 ± 17 years. The insulinomas were distributed in the pancreatic caput (57.8 %), in the cor-



▶ **Fig. 2** **a** EUS image of a homogenous insulinoma (arrow) located in the pancreatic head; ventral to the superior mesenteric-portal venous (SMPV) confluence (*). **b** EUS image of a non-homogenous insulinoma (arrow) located in the pancreatic head; the tumor has a hyperechoic margin in the form of a fat capsule; ventral to the superior mesenteric-portal venous (SMPV) confluence (*).; **volume (cm^3)**; Mean 2.3; Median 1.2; Standard deviation 2.9; Minimum 0.1; Maximum 14.2.

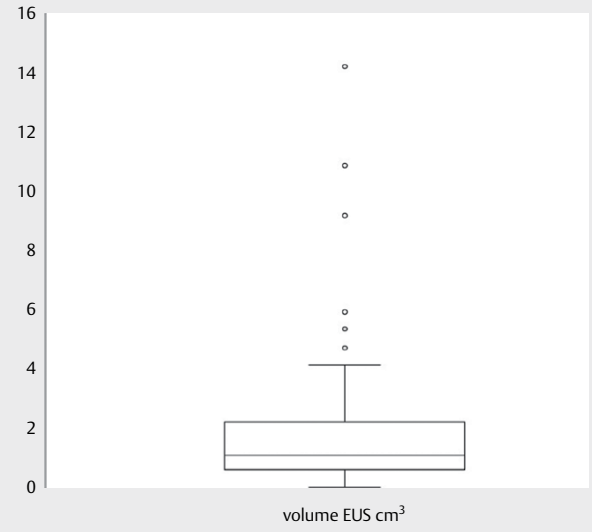
pus (17.8 %), and in the cauda (24.4 %). All insulinomas were confirmed by cyto-/histopathological analysis. Just one insulinoma was classified as malignant because of lymphogenic metastasis, and five patients were suffering from multiple endocrine neoplasia 1 (MEN 1).

Most insulinomas were small, with a median of 1.15 cm^3 (▶ **Fig. 3**). The median duration of the 72-hour fast was 10 hours, with one test that lasted over the entire duration of 72 hours. At the end of the 72-hour fast, the hormone levels were widely distributed (▶ **Table 2**).

No significant relationship was observed between the size of insulinoma measured endosonographically, the duration of a 72-hour fast, and the measured hormone levels. The AUCinsulin of the 5-hour OGTT also showed no correlation with the size of the insulinomas. The curves of the mean values of insulin and glucose showed an almost parallel progression, although the standard deviations were very large (▶ **Fig. 1**).

The endosonographic assessment of the tumor texture revealed that 31 (69 %) had a homogeneous echotexture, whereas the remaining 14 were non-homogeneous.

Non-homogeneous insulinoma were significantly larger and had a higher Ki-67 index, ranging from G1 (≤ 2 %) to G2 (3–20 %). There was no statistically substantial difference in the other values considered, not even in the subgroup analysis related to the AUCinsulin. However, each median of the hormone levels was higher in the homogeneous group, although not statistically significant. In the case of homogenous tumors, there was a tendency toward a shorter duration of the 72-hour fast (▶ **Table 3**).



▶ **Fig. 3** The distribution of the volumes measured.

▶ **Table 2** The hormone-levels measured at the end of the fast.

	Insulin mULl	C-peptide µg/L	Proinsulin pmol/L
Mean	23.6	3.2	90.4
Median	14.7	2.6	40.3
Standard deviation	25.3	2.1	198
Minimum	2.2	0.3	5.70
Maximum	124	9.7	1059

▶ **Table 3** Comparison between homogenous and non-homogenous tumors with regard to the duration of the fast, hormone levels, and Ki-67 index (medians).

	Homogenous	Non-homogenous	P-value *
n	31	14	
Volume (cm^3)	1.02	2.69	***0.007***
Duration (h)	10	12.5	*0.197*
Insulin (mU/l)	15.9	13.3	*0.508*
C-peptide (µg/L)	2.7	2.55	*0.975*
Proinsulin (pmol/l)	44.2	36.3	*1*
Ki-67 (%)	1	2	***0.01***
	subgroup analysis AUCinsulin		
N	7	9	
AUCinsulin (mU/L * min)	13729	15267	*0.681*

Discussion

Neuroendocrine tumors cause symptoms due to the autonomic secretion of hormones that lead to specific symptoms such as spontaneous hypoglycemia.

Although studies of the sizes and biochemical behavior of these lesions are common [17, 18], only a few investigations have correlated symptoms and size. This study has shown that there is no association between tumor size and severity of the disease by comparing parameters using endosonographic insulinoma measurements and description of echotexture and the characteristics of the 72-hour fast as the gold standard of diagnosis. The absolute number of hours this test lasted is probably the best marker for the patient discomfort and the severity of the disease.

The distribution of age, sex, and the fact that most insulinomas were small, show that the examined cohort in this study is representative [19]. Even though this cohort had some large tumors, just one insulinoma was classified as malignant due to metastases. This somehow contradicts the description in current guidelines [7]. However, some case reports have also been published about giant insulinoma that demonstrate the same benign behavior [20, 21].

EUS is often found to be the most sensitive localization technique for the detection of neuroendocrine tumors of the pancreas [22]. Due to its dynamic mode, the investigator can examine the tumor from different angles and positions so that the size, in particular of small tumors (< 20 mm) can be precisely determined. In addition, EUS shows an "in vivo" picture of the lesion, since the blood supply to the tumor is interrupted after the surgical resection, with the possibility that the pathologist may have a smaller diameter as a result [23]. The Center for Endocrinology, Diabetology & Osteology of Philipps-University Marburg has experience with the application of this method, which has been performed by one physician (phk) for decades. Self-reported data has shown that the detection rate is up to 88 % [24].

Attempts in the past to show a correlation between tumor size and the outcome of a 72-hour fasting gave mixed results. Wolf et al. 2015 showed a positive relationship between Ki-67 index and hormone levels, a shorter fasting test, and the size of insulinoma. However, they used modified cut-off values for the Ki-67 index [14]. Two years later, Donegan et al. published a study that found a relationship between tumor size and the duration of a 72-hour fast [13]. They used a maximum diameter and no further description of, the texture of the tumor, for example.

Our data suggest that there is no relationship between the volume and the clinical and biochemical behavior of the tumor. This corresponds with studies on other neuroendocrine tumors, for example, ACTH-secreting pituitary adenomas [25]. We found out that homogenous insulinomas are usually small and there is an indication for a shorter fasting period; on the other hand, bigger tumors have a non-homogenous echotexture and are not so hyperfunctioning, independent of the KI-67 index. Similar results were shown by Buetow et al., who described that large tumors are mostly cystic and necrotic and not hyperfunctioning [26]. Insulinomas represent a heterogenous group of tumors that show a different secretory behavior, for example, due to changes in the growth behavior of beta cells, abnormalities in the somatostatin receptor expression, or the exocytosis of the insulin granules [27]. In addition, the presence of hexokinase I enables the secretion of insulin at low blood sugar levels in some insulinomas [28]. Boden et al. put forward the theory that insulinomas mainly show glucose transporter type 1 (GLUT1) expression and healthy beta cells, mainly GLUT2 [29]. By doing this, they explained that insulinomas can secrete insulin even when glucose levels are low. However, due to more recent findings, this must be viewed critically, as GLUT2, in contrast

to GLUT1 and 3, play a rather subordinate role in humans [30]. The evaluation of the OGTT over 5 hours also showed that 50 % of the patients developed hypoglycemia after the glucose exposure. This also confirms the different secretion profiles of the insulinomas examined. This is in line with several past observations [31, 32]. Wiesli et al. 2004 described two patients with insulinoma who had a negative 72-hour fast but exhibited hypoglycemia after glucose exposure. They concluded that, in these cases, it was not an incorrect glucose sensing that was responsible for hypoglycemia but rather an excessive insulin response to glucose exposure [32].

Due to this heterogenicity, the correlation of the hormone values can only be used to a limited extent because not only the amount of insulin released is responsible for the hypoglycemia, but also insulin is released at all when glucose levels are low [33]. Since insulin is known to inhibit counter-regulatory hormones, especially glucagon, this leads primarily to hypoglycemia [34–36]. This is also reflected by the wide range of insulin, C-peptide, and proinsulin measured that all led to hypoglycemia, as well as the different secretion patterns and amounts of insulin that followed a glucose stimulus.

Based on these findings, it seems difficult to establish a connection between the size of the insulinomas and their secretory behavior because this depends on the type of cells and their potential to secrete insulin and not primarily on their number. Furthermore, we are aware that the duration of the 72-fast test depends not only on the insulin secretion but also largely on the interaction of the contra-insulin hormones such as glucagon, cortisol, catecholamines, and growth hormone [37]. This was not taken into account here. Furthermore, we have to note that, to the best of our knowledge, there are no comparable data on the AUCinsulin of the OGTT over 5 hours. These measurements are used in diabetes research [38]. Here, the OGTT insulin values are usually used over 2 hours so that the values cannot be compared with each other so that only an inter-individual comparison could be made in our study.

Another limitation of this study is that while the EUS is the most sensitive diagnostic method for neuroendocrine pancreatic tumors, it is also the most subjective. The assessment of the homogeneity was determined at the discretion of the investigator. As far as we know, there is no scaling for this, but the evaluation of whether a tumor is homogeneous or not has already been published by phk in scientific publications [39].

Since this is a retrospective work and no causality can be established on the basis of observation alone, this is a purely descriptive work.

Nevertheless, we are convinced that this investigation supports the clinical work, as we have often observed in our clinical practice that endogenous hyperinsulinism has been proven in laboratory tests, but non-invasive methods could not be used to detect insulinoma. This data supports the importance of further, perhaps also invasive, diagnostics (e. g., EUS) since small insulinomas, in particular, are difficult to identify.

In conclusion, this study contributes to answering the following question: "Does the size of the insulinoma matter?". According to our results, we can postulate that there is no connection between the measured volume and the characteristics of the 72-hour fast. Echogenicity seems to be more important than size for the expression of symptoms. These tumors are possibly well-differentiated without necrotic areas that lead to a higher and continuous insulin secretion.

Data Availability Statement

The data that supports the results (findings) of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

Jan Adelmeyer declares that there is no conflict of interest.

References

[1] Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005; 19: 753–781. doi:10.1016/j.bpg.2005.06.002

[2] Shin JJ, Gorden P, Libutti SK. Insulinoma: Pathophysiology, localization and management. Future Oncol 2010; 6: 229–237. doi:10.2217/fon.09.165

[3] de Herder WW, Niederle B, Scoazec JY et al. Well-differentiated pancreatic tumor/carcinoma: Insulinoma. Neuroendocrinology 2006; 84: 183–188. doi:10.1159/000098010

[4] Jensen RT, Cadiot G, Brandi ML et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: Functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95: 98–119. doi:10.1159/000335591

[5] Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol 2005; 19: 783–798. doi:10.1016/j.bpg.2005.05.008

[6] Cryer PE, Axelrod L, Grossman AB et al. Evaluation and management of adult hypoglycemic disorders: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94: 709–728. doi:10.1210/jc.2008-1410

[7] Rinke A, Wiedenmann B, Auernhammer C. Practice guideline neuroendocrine tumors. In: AWMF online - Das Portal der wissenschaftlichen Medizin. 2018: 56: 583–681

[8] Fendrich V, Bartsch DK, Langer P et al. Diagnosis and surgical treatment of insulinoma-experiences in 40 cases. Dtsch Med Wochenschr 2004; 129: 941–946. doi:10.1055/s-2004-823060

[9] Giannis D, Moris D, Karachaliou GS et al. Insulinomas: From diagnosis to treatment. A review of the literature. J BUON 2020; 25: 1302–1314

[10] Andreassen M, Ilett E, Wiese D et al. Surgical management, preoperative tumor localization, and histopathology of 80 patients operated on for insulinoma. J Clin Endocrinol Metab 2019; 104: 6129–6138. doi:10.1210/jc.2019-01204

[11] Martens P, Tits J. Approach to the patient with spontaneous hypoglycemia. Eur J Intern Med 2014; 25: 415–421. doi:10.1016/j.ejim.2014.02.011

[12] Nauck MA, Meier JJ. Spontanhypoglykämien. Diabetologe 2013; 9: 47–54

[13] Donegan D, Jakubikova I, Vella A. Anthropometric features are not predictive of 72-hour fast duration in insulinomas. Endocr Pract 2017; 23: 923–928. doi:10.4158/EP171872.OR

[14] Wolf P, Winhofer Y, Smajis S et al. Clinical presentation in insulinoma predicts histopathological tumour characteristics. Clin Endocrinol (Oxf) 2015; 83: 67–71. doi:10.1111/cen.12777

[15] Wright DB, London K, Field AP. Using bootstrap estimation and the plug-in principle for clinical Psychology Data. J Exp Psychopathol 2011; 2: 252–270

[16] Kann PH. Endoscopic ultrasound imaging in neuroendocrine pancreatic tumors. A critical analysis. Med Klin (Munich) 2006; 101: 546–551. doi:10.1007/s00063-006-1064-2

[17] Sato Y, Hashimoto S, Mizuno K et al. Management of gastric and duodenal neuroendocrine tumors. World J Gastroenterol 2016; 22: 6817–6828. doi:10.3748/wjg.v22.i30.6817

[18] Granberg D. Biochemical testing in patients with neuroendocrine tumors. Front Horm Res 2015; 44: 24–39. doi:10.1159/000381981

[19] Okabayashi T, Shima Y, Sumiyoshi T et al. Diagnosis and management of insulinoma. World J Gastroenterol 2013; 19: 829–837. doi:10.3748/wjg.v19.i6.829

[20] Ielpo B, Caruso R, Ferri V et al. Giant pancreatic insulinoma. The bigger the worse? Report of two cases and literature review. Int J Surg Case Rep 2013; 4: 265–268. doi:10.1016/j.ijscr.2012.11.019

[21] Mittendorf EA, Liu YC, McHenry CR. Giant insulinoma: Case report and review of the literature. J Clin Endocrinol Metab 2005; 90: 575–580. doi:10.1210/jc.2004-0825

[22] Kann PH. Is endoscopic ultrasonography more sensitive than magnetic resonance imaging in detecting and localizing pancreatic neuroendocrine tumors? Rev Endocr Metab Disord 2018; 19: 133–137. doi:10.1007/s11154-018-9464-1

[23] Polenta V, Slater EP, Kann PH et al. Preoperative imaging overestimates the tumor size in pancreatic neuroendocrine neoplasms associated with multiple endocrine neoplasia type 1. World J Surg 2018; 42: 1440–1447. doi:10.1007/s00268-017-4317-8

[24] Kann PH, Rothmund M, Zielke A. Endoscopic ultrasound imaging of insulinomas: Limitations and clinical relevance. Exp Clin Endocrinol Diabetes 2005; 113: 471–474. doi:10.1055/s-2005-865752

[25] Mathioudakis N, Pendleton C, Quinones-Hinojosa A et al. ACTH-secreting pituitary adenomas: Size does not correlate with hormonal activity. Pituitary 2012; 15: 526–532. doi:10.1007/s11102-011-0362-8

[26] Buetow PC, Parrino TV, Buck JL et al. Islet cell tumors of the pancreas: Pathologic-imaging correlation among size, necrosis and cysts, calcification, malignant behavior, and functional status. AJR Am J Roentgenol 1995; 165: 1175–1179. doi:10.2214/ajr.165.5.7572498

[27] Saddig C, Goretzki PE, Starke AA. Differentiation of insulin secretion patterns in insulinoma. World J Surg 2008; 32: 918–929. doi:10.1007/s00268-007-9450-3

[28] Henquin JC, Nenquin M, Guiot Y et al. Human insulinomas show distinct patterns of insulin secretion in vitro. Diabetes 2015; 64: 3543–3553. doi:10.2337/db15-0527

[29] Boden G, Murer E, Mozzoli M. Glucose transporter proteins in human insulinoma. Ann Intern Med 1994; 121: 109–112. doi:10.7326/0003-4819-121-2-199407150-00005

[30] Berger C, Zdzieblo D. Glucose transporters in pancreatic islets. Pflugers Arch 2020; 472: 1249–1272. doi:10.1007/s00424-020-02383-4

[31] Kar P, Price P, Sawers S et al. Insulinomas may present with normoglycemia after prolonged fasting but glucose-stimulated hypoglycemia. J Clin Endocrinol Metab 2006; 91: 4733–4736. doi:10.1210/jc.2006-1430

[32] Wiesli P, Schmid C, Perren A et al. Hypoglycemia in response to glucose and glucagon in insulinoma patients with a negative prolonged fast: Functional and morphological properties. J Endocrinol Invest 2004; 27: 832–838. doi:10.1007/BF03346277

[33] Liao J, Ding F, Luo W et al. Using the secretion ratios of insulin and C-peptide during the 2-h oral glucose tolerance test to diagnose insulinoma. Dig Dis Sci 2021; 66: 1533–1539. doi:10.1007/s10620-020-06379-z

[34] Kittah NE, Vella A. Management of endocrine disease: Pathogenesis and management of hypoglycemia. Eur J Endocrinol 2017; 177: R37–R47. doi:10.1530/EJE-16-1062

[35] Boyle PJ, Shah SD, Cryer PE. Insulin, glucagon, and catecholamines in prevention of hypoglycemia during fasting. Am J Physiol 1989; 256: E651–E661. doi:10.1152/ajpendo.1989.256.5.E651

[36] Nessa A, Rahman SA, Hussain K. Hyperinsulinemic hypoglycemia - The molecular mechanisms. Front Endocrinol (Lausanne) 2016; 7: 29. doi:10.3389/fendo.2016.00029

[37] Davis MR, Shamoon H. Deficient counterregulatory hormone responses during hypoglycemia in a patient with insulinoma. J Clin Endocrinol Metab 1991; 72: 788–792. doi:10.1210/jcem-72-4-788

[38] Ishigaki H, Yoshida A, Araki O et al. Prolonged plasma glucose elevation on oral glucose tolerance test in young healthy Japanese individuals. Endocrinol Diabetes Metab 2020; 3: e00098. doi:10.1002/edm2.98

[39] Kann PH, Ivan D, Pfützner A et al. Preoperative diagnosis of insulinoma: Low body mass index, young age, and female gender are associated with negative imaging by endoscopic ultrasound. Eur J Endocrinol 2007; 157: 209–213. doi:10.1530/EJE-07-0117

[40] Service FJ. Hypoglycemic disorders. N Engl J Med 1995; 332: 1144–1152. doi:10.1056/NEJM199504273321707