DOI: 10.4274/tjem.2613

Clinical Management of Insulinomas: A Single Institution's Experience

İnsülinomaya Klinik Yaklaşım: Tek Merkez Deneyimi

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Abstract

Purpose: Although very rare, insulinomas are the most commonly occurring endocrine tumor of the pancreas. The aim of this study was to review the clinical presentation, diagnostic approach and management of patients with insulinoma.

Material and Method: Twenty-two insulinoma patients aged between 20 and 79 years were included in the study. The subjects were evaluated according to their clinical presentation, blood biochemistry, imaging studies, operative management, pathological manifestations, postoperative and follow-up outcomes.

Results: We evaluated our medical records of patients who were internalized and underwent a supervised 72-hour fast between 2005-2011 years. Diagnosis of insulinoma was determined in 22 patients [female/male=14/8] by hyperinsuliemia during hypoglycemic episode and was assured in 21 patients with histological investigation after operation. A pancreatic mass was observed on transabdominal ultrasonography or computed tomography in 18 of the 22 [81.8%] patients preoperatively. Postoperative complications, such as postoperative cyst and intra-abdominal infection were observed in six patients.

Discussion: High serum insulin levels during hypoglycemic episode is highly specific for the diagnosis of insulinoma. Ultrasonography and computed tomography appear to be a substantially useful preoperative investigation procedure for localizing a pancreatic adenoma. In unexperienced hands, intraoperative ultrasonography is not highly conclusive procedure for pancreatic tumor localization. *Turk Jem 2014; 18: 79-83*

Key words: Insulinoma, hypoglycemia, insulinoma localization, surgical approach
Conflict of interest: The authors reported no conflict of interest related to this article.

Özet

Amaç: İnsülinoma nadir olsa da pankreasın endokrin tümörleri içerisinde en sık görülenidir. Bu çalışmanın amacı, insülinomalı hastaların klinik prezentasyonlarının, tanısal yaklaşımlarının ve takiplerinin değerlendirilmesidir.

Gereç ve Yöntem: Yaşları 20-79 arasında olan, yirmi iki insülinomalı hastanın klinik prezentasyonları, biyokimyasal ölçümleri, görüntüleme çalışmaları, operasyon yaklaşımları, patolojik buguları, postop dönem ve uzun süreli takipleri değerlendirilmiştir.

Bulgular: 2005-2011 yılları arasında yatırılmış ve 72 saatlik uzun açlık testi yapılmış hastaların medikal kayıtları incelendi. Hipoglisemi sırasında hiperinsülinizm 22 hastada (kadın/erkek=14/8) saptanarak insülinoma tanısı konulmuş ve 21 hastada operasyon sonrası histolojik değerlendirme yapılmıştır. Preoperatif olarak 22 hastanın 18'de (%81,8) transabdominal ultrasonografi veya tomografi ile pankreasta kitle saptanmıştır. Altı hastada kist ve intraabdominal enfeksiyon gibi postop komplikasyon saptanmıştır.

Tartışma: Hipoglisemik episod esnasında yüksek serum insulin düzeyleri insülinoma tansı için oldukça spesifiktir ve ultrasonografi ve tomografi pankreatik adenomların lokalize edilmesinde kullanışlı preoperatif inceleme yöntemleridir. Deneyimsiz merkezlerde intraoperatif ultrasonografi pankreastaki tümörlerin localize edilmesinde çok uygun değildir. *Turk Jem 2014; 18: 79-83*

Anahtar kelimeler: İnsülinoma, hipoglisemi, insülinoma lokalizasyonu, cerrahi yöntem
Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

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Introduction

Despite the most common functional islet tumors, insulinomas are uncommon with an incidence of four cases per million per year (1). Pancreatic endocrine tumors are generally indolent and frequently go unnoticed. The number of reported cases has been increasing due to the development of advanced radiographic techniques and familiarity by physicians. Surgery is the treatment of choice and offers high opportunity of cure (2,3).

Patients with insulinoma usually present with episodic symptoms of hypoglycemia that could be mistaken for a neuropsychiatric disorder. The diagnosis of hyperinsulinemic hypoglycemia is established by demonstrating inappropriately high serum insulin concentrations during hypoglycemia (4). Even after biochemical confirmation, localization of the tumor before or during surgery can be challenging.

Retrospective review of adult patients with insulinoma treated at Uludağ University Medical Center from 2005 to 2011 is presented in this study. We performed an audit of our management of insulinoma patients. This paper discusses clinical presentation and diagnosis of insulinoma with surgical cure results.

Materials and Methods

During a period from 2005 to 2011, a total of 22 patients diagnosed with insulinoma were included in this retrospective study. Hyperinsulinemic hypoglycemia was shown in each patient with a plasma insulin level of more than 3 μIU/mL, meanwhile a glucose level of less than 45 mg/dL and in patients who had hypoglycemic symptoms. The clinical presentations, biochemical results, preoperative localization results, surgical approaches, pathological findings, postoperative complications, and follow-up results of patients were analyzed. The study protocol was approved by the Ethics Committee of Uludag University Medical Faculty.

Computed tomography (CT) was the preferred and mostly applied imaging method for the preoperative localization of the tumor in our center. Abdominal ultrasonography (US) was done for most of the patients. Intraoperative US (IOUS) was performed only when these imaging techniques failed to demonstrate a lesion. All patients, except one who refused, underwent surgery.

Insulin was measured by automated electrochemiluminescence immunoassay provided by Roche Diagnostics (Roche Diagnostics GmbH, Mannheim, Germany). The lower detection limit of the assay is 0.02 μIU/mL. The inter- and intra-assay coefficients of variation are 3.7% and 4.6%, respectively. The normal range for fasting serum levels is 2.6-24.9 μIU/mL.

All the quantitative data is expressed as mean ± standard deviation. Categorical variations were summarized using proportions. The sensitivity was calculated using standard formula (sensitivity=true positive/true positive+false negative).

Results

The majority of the patients were female (65.2%) with a mean age of 53.0±18.8 years at the time of diagnosis (Table 1). All patients presented with histories suggestive of hypoglycemia while two of them were recurrent insulinoma patients who had been operated 5 and 8 years ago. Most of the patients had had minor neurogenic and neuroglycopenic symptoms while 7 of them (30.4%) had had severe neuroglycopenic symptoms, such as loss of consciousness and seizures. They stated that the duration of symptoms before the diagnosis was 14.3±24.4 months (range: 1 to 120 months).

The mean morning fasting blood glucose level was 72.4±18.3 mg/dL and only 6 patients had blood glucose levels less than 60 mg/dL. None of the patient had a HbA1c level of less than that within normal range. Fasting blood insulin level and C-peptide level were within normal ranges in all aptients. All the patients were admitted to the medical center and underwent supervised 72-hour fast. They all developed symptomatic hypoglycemia within the first 40 hours of the fast. Four of them developed symptomatic hypoglycemia in 3 hours, 9 of them in 3-12 hours, 8 of them in 12-24 hours, and only 1 patient developed hypoglycemia in more than 24 hours, at 40th hour (Figure 1). Diagnosis of insulinoma was proven biochemically with a plasma insulin level of ≥3 μIU/mL while glucose level was <45 mg/dL with neuroglycopenic symptoms. The mean serum insulin level during hypoglycemia was 22.0±14.2 μIU/mL with highest and lowest levels of 61 μIU/mL and 4 μIU/mL, respectively.

Computed tomography is the preferred and mostly applied imaging method for preoperative localization of the tumor in our

Table 1. Demographic/clinical characteristics and imaging procedures of patients with insulinoma

Demography	
Age (years)	53.0±18.8
Male: Female	9:13 (1:1.85)
Sporadic insulinoma	22/22 (100%)
Clinical	
Duration of symptoms (months)	14.3±24.4
Patients experienced lifethreating symptoms	7/22 (31.8%)
Diagnostic imaging	
Localized by US	9/14 (64.3%)
Localized by CT	13/21 (61.9%)
Localized by US and/or CT	18/22 (81.8%)
Localized by intraoperative US	2/4 (50%)

Table 2. Procedures of surgery and histological features of insulinoma (n=21)

Type of performed surgery	
Tumor enucleation	17 (810%)
Distal pancreatectomy	2 (9.5%)
Distal pancreatectomy and splenectomy	2 (9.5%)
Histology	
Presence of two lesions	1 (4.7%)
Tumor size ≥2 cm	5 (23.8%)
Angio-invasiveness	0 (0%)
Ki-67 index > 2%	9 (42.9%)
Presence of distant metastases	0/21 (0%)

center. Trans-abdominal US was also performed in most of the patients. Pancreatic mass could be localized in 13 of 21 (61.9%) patients by CT and in 9 of 14 (64.3%) patients by transabdomial US (Figure 2, 3). In a total manner, pancreatic mass was localized in

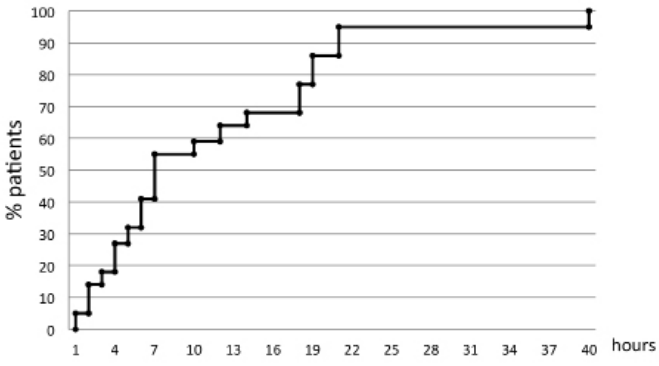

Figure 1. Percent of patients encountering hypoglycemia during supervised fast according to time periods

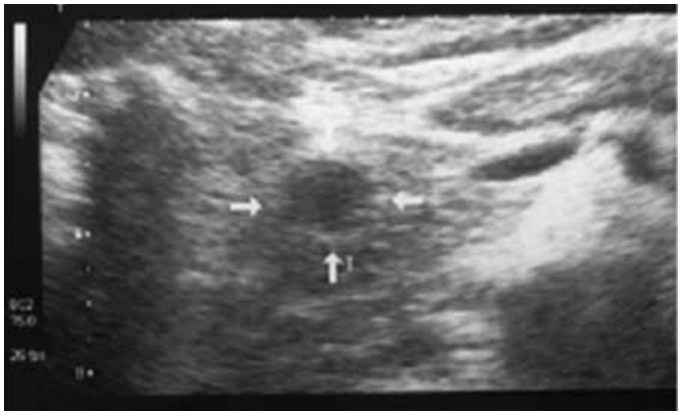

Figure 2. Ultrasonographic image of the patient shows a hypoechoic solitary lesion on the head of the pancreas as that an insulinoma

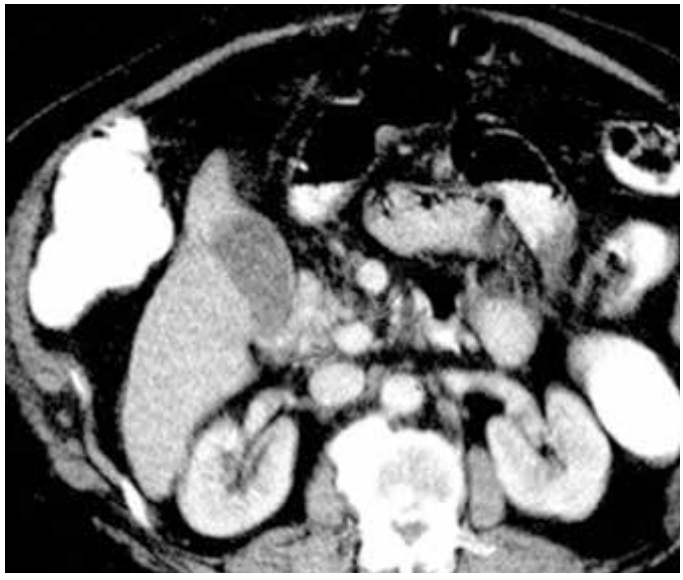

Figure 3. CT image of one patients shows hyperdense nodule is seen within posteromedial portion of pancreatic head

18 of 22 (81.8%) patients preoperatively by US and/or CT (Table 1). Selective arteriography, venous sampling during arterial stimulation or endoscopic US are unavailable imaging techniques in our center. IOUS was performed in only patients in whom tumors could not be localized preoperatively. Intraoperative ultrasonographic evaluation was performed in 4 patients, mass was found in only 2 of them.

One patient did not give consent for surgery. She is on follow-up visits for about 15 months. She had had one moderately severe hypoglycemic attack in this period. The rest of the patients underwent an open technique abdominal surgical procedure. Postoperatively, all the patients, except one, were without any hypoglycemic symptom and were supposed to be cured clinically. In one patient, pancreatic mass could not be found during operation; symptoms persisted after surgery. She had undergone a second operation after a short time by accompaniment of other surgeons. Her mass was found in the head of the pancreas. The locations of the tumors were distributed as follows: 10 of them (45.5%) were in the head, 6 - (27.3%) in the body, 3 - (13.7%) in the uncinate process, and 3 of them (13.7%) were in the tail of the pancreas. One patient had 2 tumors which both were located in the body of the pancreas.

Enucleation was performed in 17 patients (81.0%) if the lesion was clearly localized and was small. Distal pancreatic resection was needed in 4 patients. Most of the lesions measured 1-2 cm in diameter, where only 5 of them (23.8%) were more than 2 cm and 2 of them (9.5%) were smaller than 1 cm (Table 2).

Postoperative complications were observed in 6 patients (28.5%). In two patients, pancreatic cyst evolved postoperatively. One of them required reoperation for cyst aspiration. Two patients had intra-abdominal infection which caused by the longer hospital stay. Except these two patients, all patients were discharged within 8.2±3.9 days. Patients with abdominal infection were discharged 32 and 42 days after surgery. After discharge, 2 patients were rehospitalized, one due to infection and one patient for evisceration.

Immunohistochemical examination showed that all specimens stained strongly with insulin dye. Only one patient had multifocality. No invasion was observed to the adjacent organs. Histopathological investigation of the tumor revealed no angio-invasivasion. Ki67 staining showed ≤2% positivity in 9 of them and >6% positivity in two patients (9.5%) and the rest showed any value amongst (Table 2). Two patients with recurrent insulinomas did not have any angio-invasive feature. Their adenoma sizes were 1.2 cm and 1.8 cm and Ki-67 positivity ratios were 5% and 7%, respectively.

The mean postoperative follow-up period was 28.4±27.1 months. Eight patients were lost to follow-up. No recurrence or metastasis was detected. All patients were questioned or biochemically evaluated for multiple endocrine neoplasia during the follow-up period. We did not observe any finding resembling multiple endocrine neoplasia.

Discussion

Classical symptoms of Whipple's triad suggest the diagnosis of insulinoma. Most patients with insulinoma have hypoglycemic

symptoms in the postabsorptive state. However, clinicians should be aware that postprandial hypoglycemia can be the manifestation of an insulinoma (5). Since prolonged fasting can be the only occasion of hypoglycemia in some of insulinoma patients, challenging for hypoglycemia should be extended for 72 hours (6). Definitive diagnosis of insulinoma should be established by inappropriately high plasma insulin level during low serum level of blood glucose (6,7).

Twenty-two patients with biochemically diagnosed insulinoma were included in this study. The mean age at presentation was 53.0±18.8 years with a range between 20-79 years. Forty-six percent of patients were older than 60 years while 18% were younger than 30 years. Male/female ratio (1/1.85) was similar in all age groups.

All patients had symptoms of hypoglycemia, some with minor but some with severe manifestations. It was striking that most patients had hypoglycemic symptoms more than a year; some had even more than 10 years. Thirty percent of patients reported major hypoglycemic episodes with unconsciousness or convulsion (8,9). There was no patient reporting early postprandial hypoglycemia. Most of the patients had been diagnosed with anxiety, panic disorder, menopausal symptoms, transitional ischemia, arrhythmia or epilepsy. Two patients were admitted due to recurrence of hypoglycemic symptoms 5 and 8 years after surgical treatment of insulinoma.

Preoperative localization of the tumor is desirable for determining the most appropriate surgical approach and to obviate blind pancreatectomy (10). It offers some degree of comfort to both the surgeon and patient prior to entering the operating room. Since any imaging modality (transabdominal US, CT, MRI, angiography, intra-arterial calcium stimulation with venous sampling, endoscopic US and somatostatin receptor scintigraphy, positron emission tomography) could not attain high sensitivity, besides cost, invasiveness of the imaging techniques; institutional preferences differs widely (4,10).

In our center, CT is the preferred imaging technique for pancreatic endocrine tumors. CT is a safe, widely available and mostly used initial noninvasive technique for localizing insulinomas (10). A wide range of sensitivities have been reported with CT scanning from 16% to 72% (10,11). CT was utilized almost in all patients except one in whom pancreatic mass was undoubtedly identified by US. Calculated sensitivity of CT was 64% in our series.

Transabdominal ultrasonographic evaluation was performed in 14 patients and resulted with a sensitivity of 64% which is better than most of the reported results (12,13). Sensitivity of US is highly operator-dependent and US examination has limitations based on body habitus (10,12,13). With combination of CT and US, preoperative localization of the tumor was reached in 18 patients with a sensitivity rate of 81.8% which is higher than many recommended invasive or costly procedures.

For definite tumor localization, some centers recommend IOUS for all insulinoma patients. It has been reported that especially in pancreatic head tumors, IOUS sensitivity was almost 100% (14,15). Because in our medical center IOUS examination is not a routine procedure for an insulinoma patient, it was performed in only 4 patients in whom pancreatic mass could not be distinguished preoperatively. In 4 patients, tumor was identified only in 2 of them, 1 in the head and 1 in the tail. But in the other 2 patients tumors could not be found by IOUS, in whom tumors were detected both in the head of the pancreas by palpation and were resected. Sensitivity of IOUS was calculated as 50% which is strikingly low compared to reported results. This low sensitivity with this technique is most probably due to our low experience.

Surgical treatment of insulinomas is safe and curative in most patients (16,17). The choice of the surgical approach depends on tumor size and localization. Enucleation is the preferred surgical procedure because it preserves normal parenchyma with few complications (1,4,18). Even if tumor is localized preoperatively by imaging techniques, bidigital palpation by an experienced surgeon and IOUS is recommended to localize the tumor in certain and also to determine if there are existing additional tumors (19,20). If the plane between tumor capsule and the pancreatic parenchyma cannot be easily identified, enucleation could not be performed safely (19). A distal or segmental pancreatectomy is generally performed., Blind distal pancreatectomy has been performed for years when the tumor was not seen or palpated (21). According to this method, after the removal of distal pancreas, the specimen is sliced by a pathologist in thin cuts to look for the tumor. If the tumor is not found, then the pancreas is excised until 80% of the pancreas has been removed (21). However, today, it is known that blind distal pancreatectomy may fail in a somewhat high ratio of the patients. With current preoperative and surgical advances, blind distal pancreatectomy is not a logical approach (22). In the event that no tumor can be identified during operation, a blind distal pancreatic resection should be avoided.

In our series, enucleation was accomplished in 17 patients (81%), where 4 patients had some kind of pancreatic resection with or without splenectomy. Only in one patient (4.7%) 2 lesions were detected. Although these operations were performed not only by one surgeon, fortunately, most of the patients achieved cure after surgery. Even it is reported that 10% of insulinomas are malign, and 15% of them are associated with multiple endocrine neoplasia type 1, we did not find any (23). Only one patient necessitated second operation very soon and, successful outcome was achieved.

Although all the tumors were positive for insulin staining immunohistochemically in this study, many studies have showed that substantial percent of insulinomas may have negative insulin dye results (24). It has also been reported that immunohistochemical results are not directly correlated with insulin secretion capacity and final diagnosis of insulinoma should not depend on the result of insulin dye examination (25). Final diagnosis of insulinoma is settled by preoperative hyperinsulinemia, pathological result of pancreatic neuroendocrine tumor and postoperative improvement of hypoglycemic symptoms (1,4,26).

The World Health Organization classifies neuroendocrine tumors of the pancreas into 3 categories: well-differentiated neuroendocrine adenoma, well-differentiated neuroendocrine carcinoma and poorly-differentiated neuroendocrine carcinoma (27). Since we did not observe any metastasis or any invasion of the adjacent organs, all the tumors were classified as well-differentiated

neuroendocrine tumor. Well-differentiated neuroendocrine tumors may be sub-classified as benign or low-grade malignant due to tumor size, angio- or neuro-invasiveness, mitoses count or Ki-67 positivity ratio (27). Cut-points are ≥2 cm adenoma size, vascular invasion, perineuroal invasion, >2 mitoses/10 HPF or >2% Ki-67 positive cells (27). Tumors showing any of these criteria are supposed to be well-differentiated neuroendocrine tumor with uncertain malignant potential. In contrast to the other types of pancreatic endocrine tumors, the vast majority of insulinomas are benign (28,29). The percentage of malignant insulinoma ranges from 2.4 to 17.9 in the reported series (30). There is no specific morphologic, biochemical or genetic features that distinguish benign from malignant tumors. Documentation of metastatic disease is the only proof of a malignant insulinoma (29,31).

In our series histopathological examination did not reveal any angio-invasiveness. But many of our patients had features resembling uncertain malignant potential. Adenoma size greater than 2 cm was found in 5 patients (23.8%), Ki-67 positivity more than 2% was found in 9 patients (42.9%). These are not distinctive features of a pancreatic tumor that predicts a subsequent metastasis. Two patients were operated because of recurrence after 5 and 8 years. Although their repetition, they did not have enough criteria for diagnosing malignant insulinoma.

Conclusion

Our results show that all patients with insulinoma develop hypoglycemia within 40 hour of fasting. Transabdominal US and CT localize the insulinoma in most patients. IOUS and bidigital palpation can help localize tumors that could not be distinguished preoperatively, but they are highly operator- and experience-dependent. Surgical resection is the only potentially curative treatment option for patients. Although the choice of surgical approach depends on tumor characteristics, enucleation is the preferred surgical procedure. For the classification of benign or low-grade malignant neuroendocrine tumors of the pancreas, tumor size, angio- or neuro-invasiveness, mitoses count or Ki-67 positivity ratio could all be used. However, it should be kept in mind that they are not highly specific or sensitive measures. It is well known that the presence of metastatic disease is the only proof of a malignant insulinoma.

Conflicts of Interest

There are no conflicts of interest.

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