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The incidence of insulinoma in Western Sweden between 2002 and 2019

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Abstract

Background Insulinoma is a rare pancreatic neuroendocrine neoplasm with an incidence of 0.7-4 cases per million/year. Because of its rarity, epidemiological studies on insulinoma are few and limited by small sample sizes. An increasing incidence of insulinoma has recently been suggested. The primary aim of this study was to investigate the incidence of insulinoma in the Västra Götaland Region (VGR) of Sweden. Secondary aims were to evaluate clinical characteristics, diagnostic workup, management and outcome in patients diagnosed with insulinoma.

Methods Medical records were reviewed for all patients in the VGR who had received an ICD-10 diagnosis code of a benign (D13.7) and/or a malignant (C25.4) tumor in the endocrine part of the pancreas, of hypoglycemia (E.161), and/or a code of a fasting test (AB011), from 2002-2019.

Results Forty-two patients with insulinoma were identified, 37 of whom (20 men) were residents in the VGR at the time of diagnosis, giving a mean annual incidence of 1.3 cases per million/year. The mean (±standard deviation) age at diagnosis was 56±18 years. Six of the 37 (16%) patients had metastatic insulinoma and 2 patients (5%) had a confirmed multiple endocrine neoplasia type 1 syndrome. At preoperative workup, computed tomography and endoscopic ultrasound detected an insulinoma in 28/36 (78%) and 21/21 (100%) cases, respectively.

Conclusions Insulinoma remains a rare tumor in the modern era. The recorded mean annual incidence of 1.3 cases per million/year is compatible with the reported incidence in Sweden during the 1980s. Our results do not support an increasing incidence of insulinoma.

Keywords Insulinoma, epidemiology, incidence, fasting test, epilepsy

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Introduction

Pancreatic neuroendocrine neoplasms (Pan-NENs) constitute a group of rare neoplasms [1] classified as either functioning or non-functioning, depending on their clinical manifestation [2]. Insulin-producing tumors, insulinomas, are the most common functioning Pan-NENs [2]. Because of their rarity, epidemiological studies on insulinoma are few and, apart from a recent study from Japan [3], most often limited by small sample sizes [4-7]. Available studies, almost all published in the late 1980s and early 1990s, showed an incidence varying between 0.7 and 4 cases per million/year [3-7].

Recently, an increasing incidence of Pan-NENs has been suggested [2,8,9]. Regarding insulinomas in particular, a recent study from Finland recorded an increasing incidence, from 0.5 cases per million/year in the 1980s to 0.9 cases per million/year in the 2000s [10]. Nevertheless, data on

the epidemiology of insulinoma in the modern era are scarce, and it is still unclear whether the incidence is truly increasing, as it is for some other hormone-producing tumors like pheochromocytoma [11,12] and aldosterone-producing adrenal adenoma [13].

The preoperative diagnosis of insulinomas is challenging. The tumors are often small and difficult to detect by routine computed tomography (CT) [14,15]. Endoscopic ultrasound (EUS) is very suitable for close-up imaging of pancreatic lesions. In addition, EUS enables fine-needle aspiration of Pan-NENs [16]. Nonetheless, there is a lack of data on the relative sensitivity of CT and EUS for insulinoma detection.

The primary aim of this study was to investigate the annual incidence of insulinoma in the Västra Götaland Region (VGR) in Sweden between 2002 and 2019. Secondary aims were to describe the clinical characteristics and diagnostic workup in patients with insulinoma, to evaluate the sensitivity of CT and EUS in the detection of insulinoma, and to investigate the clinical outcome.

Materials and methods

This was a retrospective study conducted at the Sahlgrenska University Hospital in Gothenburg. All patients in the VGR with suspected insulinoma are referred to the Sahlgrenska University Hospital for further evaluation, workup and treatment. At the beginning of the study period (January 1st 2002), according to the Swedish National database of statistics, the VGR had a population of 1,507,614 individuals. At the end of the study period (December 31st 2019), the population was 1,724,529 individuals (mean 1,595,917).

The study was conducted according to the declaration of Helsinki and was approved by the Regional Ethics Committee of West Sweden, Gothenburg, Sweden (DNR 814-18).

Identification of patients and data collection

Any diagnosis recorded at a patient visit to any Swedish hospital is coded in a diagnosis-related group (DRG) registry. To identify patients with insulinoma, the DRG registry at the Sahlgrenska University Hospital was searched for the following ICD-10 codes (recorded between January 1st 2002 and December 31st 2019): D13.7 (benign neoplasm in the endocrine part of the pancreas), C25.4 (malignant neoplasm in the endocrine part of the pancreas) and E16.1 (other hypoglycemia), and/or the following workup code: AB011 (fasting test). Medical records of all identified patients were reviewed and information was collected on clinical, biochemical, radiological and histopathological findings, as well as management and outcome. In addition, the duration of symptoms before diagnosis was estimated through chart review, based on the patient's own description of symptoms consistent with an insulin-producing Pan-NEN.

Biochemical workup and fasting test

The results from a supervised fasting test were collected, including glucose in plasma, and insulin and C-peptide in serum. In patients with a confirmed insulinoma, who did not undergo a supervised fasting test, the lowest recorded spontaneous plasma glucose level was recorded, as were the corresponding insulin and C-peptide levels in serum.

The same 72-h fasting test protocol, which is the gold standard for confirmation of insulinoma [17-19], was used during the entire study period. The fasting tests started at 7 AM, after a light breakfast. During the test, symptoms indicating neuroglycopenia were continuously monitored, and plasma-glucose (P-glucose), serum-insulin (S-insulin) and C-peptide were measured every 8 h. If significant hypoglycemia (<3.0 mmol/L) developed, and was accompanied by neuroglycopenic symptoms, the test was terminated. Patients with S-insulin ≥3 μU/mL and/or C-peptide ≥0.2 nmol/L upon termination were considered to have endogenous hyperinsulinism.

Diagnostic imaging with CT and EUS

During diagnostic workup, patients were referred for abdominal CT and, at the discretion of the physician in charge, for EUS. The CT was performed with and without intravenous contrast, and by the application of recommended scanning protocols. All examinations were assessed by 2 dedicated radiologists. A CT scan was considered positive for insulinoma if the radiologists detected findings consistent with or were strongly suspicious of a Pan-NEN. The EUS examination was performed under conscious sedation, by any of the 3 experienced endosonographers at the hospital, using a linear echoendoscope (Pentax, Tokyo, Japan) and an ultrasound processor (Hitachi, Tokyo, Japan). The complete pancreatic gland was examined. An insulinoma was regarded as detected by EUS if the endosonographer recorded endosonographic findings consistent with or strongly suspicious for a Pan-NEN.

Clinical follow up

After diagnosis, management of patients was determined at a multidisciplinary therapy conference. After relevant therapy, all patients were closely monitored via biochemistry and visits to the outpatient unit for a minimum of 12 months. Any signs of insulinoma recurrence were subjected to resumed and detailed reevaluation.

Statistical analysis

Normally distributed continuous variables were represented as mean ± standard deviation and non-normally distributed variables as median (range; interquartile range [IQR]). Categorical variables were represented as n (%). For comparison between 2 groups, the unpaired *t*-test was used

for normally distributed data and the Mann-Whitney *U* test for non-normally distributed data. Pearson's chi-square and Fisher's exact test were used for comparisons between categorical variables. A 2-tailed P-value <0.05 was considered to be statistically significant. The incidence of insulinoma was calculated by dividing the total number of patients in the VGR diagnosed with insulinoma, between January 1st 2002 and December 31st 2019, by: a) the mean population (1,595,917) during the same time period; and b) the number of years constituting the study period (n=18). Patients diagnosed with insulinoma but not resident in the VGR at the time of diagnosis, i.e., patients living in other countries or other regions in Sweden, were excluded from the incidence analysis. IBM Statistics SPSS version 27 was used for the statistical analyses.

Results

The incidence of insulinoma

In total, 583 patients were identified as being assigned at least one of the above specified codes (D13.7, C25.4, E16.1, and/or AB011) (Fig. 1). Among these 583 patients, 42 were indeed diagnosed with insulinoma. Five of these 42 patients were excluded from further analysis (4 residing outside the VGR and 1 diagnosed before the study started). Thus, 37 inhabitants of the VGR, 20 (54%) men and 17 (46%) women, were diagnosed with an insulinoma between 2002 and 2019, giving a mean annual incidence of 1.3 cases per million/year. Twenty-one (57%) patients were diagnosed between 2002 and 2010 and 16 (43%) between 2011 and 2019.

Clinical characteristics of patients with insulinoma

The mean age at diagnosis was 56±18 years (range 19-86), 63±17 in women and 50±16 in men (P=0.03). Six of the 37 (16%) patients had metastatic insulinoma and 2 patients (5%) had a confirmed multiple endocrine neoplasia (MEN) type 1 syndrome. Other relevant characteristics are presented in Table 1.

Biochemical workup and fasting test

In 9 patients, the diagnosis of insulinoma was considered confirmed without a fasting test. All these patients had spontaneous hypoglycemia and neuroglycopenic symptoms, high insulin concentrations, and relief of symptoms upon administration of glucose (Whipple's triad).

In the 37 patients with insulinoma, the mean nadir P-glucose at diagnosis was 2.1±0.6 mmol/L, with no significant difference between those who underwent a fasting test (n=28) and those who did not (n=9) (P=0.7). The median (IQR) S-insulin [17 μU/mL (8-28) vs. 29 μU/mL (25-83); P=0.02] and C-peptide [1.0 nmol/mL (0.8-1.3) vs. 2.2 nmol/mL (1.5-3.0); P=0.002] were significantly lower in patients who underwent a fasting test compared to those who did not.

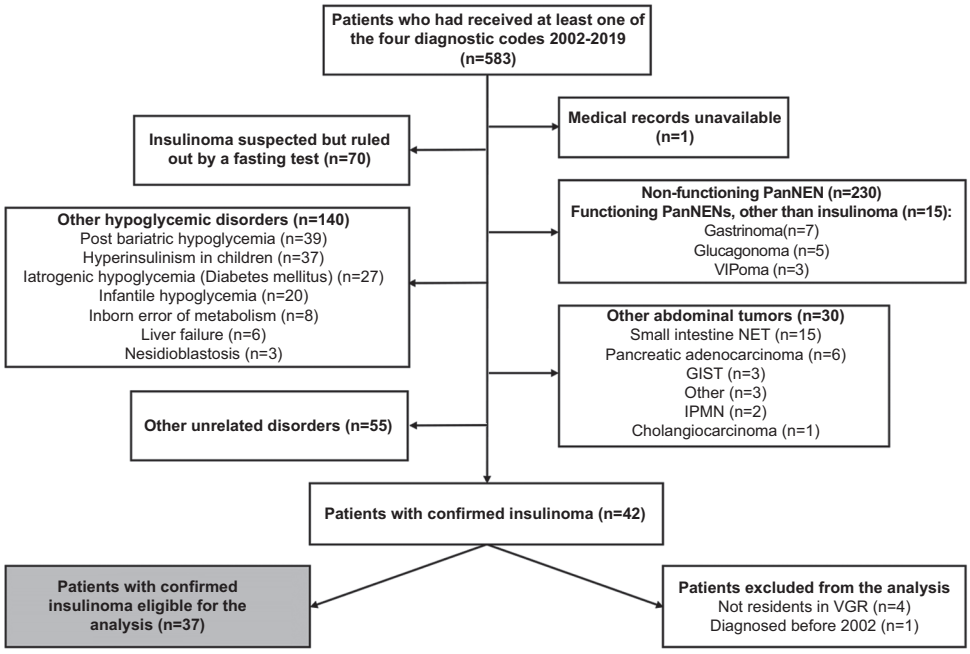

Figure 1 Summary of the final diagnoses in 583 patients who had been assigned at least one of the following diagnostic codes between January 1st 2002 and December 31st 2019: D13.7 (benign neoplasm in the endocrine part of the pancreas), C25.4 (malignant neoplasm in the endocrine part of the pancreas), and E16.1 (other hypoglycemia) and/or the following workup code: AB011 (fasting test)
GIST, gastrointestinal stromal tumor; IPMN, intraductal papillary mucinous neoplasm; NET, neuroendocrine tumor; PanNEN, pancreatic neuroendocrine neoplasm; VGR, Västra Götaland Region; VIP, vasoactive intestinal peptide

S-insulin [55 μU/mL (32-99) vs. 20 μU/mL (9-27)] and C-peptide [1.8 nmol/mL (1.3-3.5) vs. 1.0 nmol/mL (0.8-1.3) were significantly higher in patients with metastatic insulinoma compared to localized insulinoma (P=0.005 and P=0.04, respectively) (Fig. 2).

Table 1 Characteristics of the study cohort, 37 patients diagnosed with insulinoma in western Sweden from 2002-2019

Patient characteristics	Value
Age (years), mean±SD	56±18
Sex, n (female/male)	17/20
MEN-1 syndrome, n (yes/no)	2/35
Tumor characteristics	
Tumor size (at CT in mm), median (IQR)	15 (13-18)
Tumor position (head/body/tail)	16/6/15
Tumor type (localized/metastatic) *	31/6
Tumor grade, n (G1/G2/G3)	12/16/1
Clinical characteristics	
Hypoglycemia (<3 mmol/L) at presentation, n/n (%)	34/37 (92)
Neuroglycopenic symptoms before diagnosis, n/n (%)	32/37 (86)
Loss of consciousness before diagnosis, n/n (%)	11/37 (30)
Diagnosed with epilepsy before diagnosed with insulinoma, n/n (%)	3/37 (8%)
Duration of symptoms before first physician's visit, months, median (range, IQR)	2 (0-168, 0.3-17)
Time from first visit until correct diagnosis, days, median (range, IQR)	43 (6-4745, 15-199)
Time from diagnosis to treatment, days, median (range, IQR)	17 (-51-814, 6-39)

*The median Ki-67 was 9.5% (range 6.5-40, IQR 7.3-25.0) in metastatic and 2.3% (range 1.0-7.0, IQR 1.4-3.6) in localized insulinomas. The median size was 42.5 mm (range 25-60, IQR 27.5-57.5) in metastatic and 15 mm (range 8-28, IQR 12-18) in localized insulinomas

SD, standard deviation; CT, computed tomography; IQR, interquartile range; MEN, multiple endocrine neoplasia

Four of the 28 patients with insulinoma who underwent a fasting test developed significant hypoglycemia and neuroglycopenic symptoms first after more than 48 h of fasting. One further patient, eventually diagnosed with insulinoma, passed the 72-h fasting test without developing neuroglycopenic symptoms (Fig. 3).

Diagnostic imaging with CT and EUS

Thirty-six (97%) of the 37 patients with insulinoma underwent preoperative CT and 21 (57%) patients underwent preoperative EUS. A lesion consistent with, or strongly suspicious for, an insulinoma was detected by CT scan and EUS in 28/36 (78%) cases and in 21/21 (100%) cases, respectively. Among the 21 patients who underwent EUS, 20 had previously undergone a CT scan. In these 20 patients, an insulinoma was detected by both CT scan and EUS in 12/20 (60%) patients and only by EUS in 8/20 (40%) patients.

Other imaging modalities used were: magnetic resonance imaging in 18 patients, where 15 (83%) tumors were identified; somatostatin receptor scintigraphy in 9 patients, where a pathological uptake was demonstrated in 5; and Ga68-DOTATATE-PET in 5 patients, revealing a tumor in all. Selective arterial calcium stimulation was not performed in any patient.

Clinical outcomes

Among the 31 patients with localized insulinoma, 30 (97%) underwent surgical resection; 15 (50%) with resection and 15 (50%) with enucleation. R0-resection was obtained in all. One elderly patient was regarded as unfit for surgery because of comorbidities. At the time of data collection, 7 (23%) patients with localized insulinoma were deceased, all of them from unrelated causes.

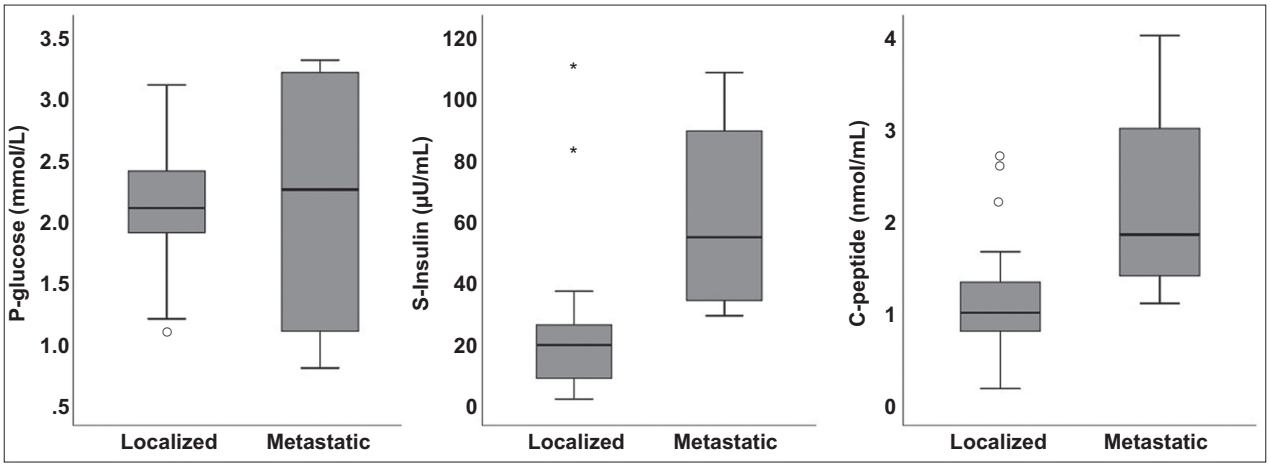

Figure 2 Box plots showing concentrations of plasma glucose, serum insulin, and serum C-peptide in patients with benign and malignant insulinoma

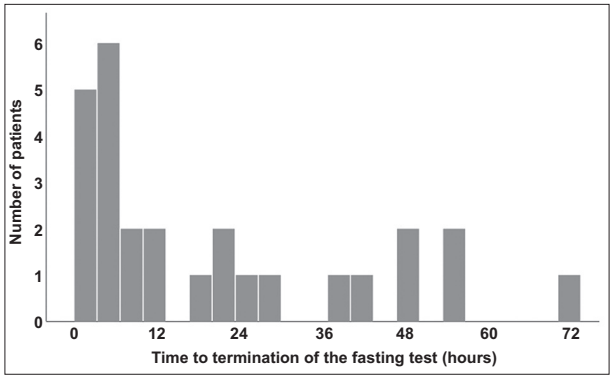

Figure 3 Histogram showing the duration of all fasting tests performed in patients diagnosed with insulinoma (n=28)

Among the 6 patients with metastatic insulinoma, 4 (67%) had metastatic disease at diagnosis (primarily to the liver). Four (67%) patients underwent surgical resection as part of a multimodal treatment protocol. R0-resection was obtained in only 1 of these 4 patients. The same patient experienced recurrent disease 6 years postoperatively. At the time of data collection, 5 (83%) patients with metastatic insulinoma were deceased, 3 of them due to the insulinoma and 1 due to unrelated reason. The cause of death was unknown in 1 patient.

Discussion

Previous epidemiological studies from Sweden [5], Northern Ireland [7] and New Zealand [4] have shown a similar annual incidence of insulinoma: between 0.7 and 1.2 cases per million/year (Table 2). However, a higher incidence has been reported in Japan [3] and the United States [6] (3.3 and 4.0 cases per million/year, respectively). In this study, analyzing all new cases with insulinoma in West Sweden between 2002 and 2019, the mean annual incidence was 1.3 cases per million/year, compatible with the reported incidence in Sweden during the 1980s [5]. Therefore, our results do not support an increasing incidence of insulinomas as previously suggested [10].

An increasing incidence of Pan-NENs (functioning tumors as well as non-functioning tumors) has been suggested [8,20,21], most probably explained by the increasing use of high-quality imaging techniques in general, where non-functioning Pan-NENs are frequently detected incidentally [9]. Thus, many of these tumors would probably have remained undiagnosed, similarly to lesions like small pancreatic side-branch intraductal papillary mucinous neoplasms [22] and small gastrointestinal stromal tumors [23]. Consequently, the true incidence of symptomatic non-functioning Pan-NENs may not be on the rise.

Our results agree with previous studies showing that insulinomas can appear at all ages, but with a peak during the 5th decade of life. Also, our results are in line with previous studies showing an equal sex distribution, or a slight predominance in women [4,6,17,24-26]. In 2 studies from the Mayo Clinic, published in 1991 and 2009 respectively, 8% and

Table 2 Summary of studies evaluating the incidence of insulinoma

Author, year of publication [ref.]	Country	Period	Number of cases	Incidence
Cullen and Ong 1987 [4]	New Zealand	1970-1985	8	0.7
Eriksson *et al* 1989 [5]	Sweden	1969-1988	23	1.1
Watson *et al* 1989 [7]	Northern-Ireland	1970-1985	21	1.2
Service *et al* 1991 [6]	USA	1927-1986	224	4.0
Peltola *et al* 2018 [10]	Finland	1980-2010	79	0.5-0.9
Kurakawa *et al* 2021 [3]	Japan	2013	148	3.3

6% of all patients diagnosed with insulinoma during 60 years had MEN-1 syndrome [6,26]. Similarly, 6% of 198 patients with insulinoma from Italy [27] and 5.7% of patients in Japan [3] had MEN-1 syndrome. Thus, the recorded rate of 5% with MEN-1 syndrome among insulinoma patients in our study is comparable to previous reports. In the current study, the insulinomas were most often found in the head (n=16, 43%) or the tail (n=15, 41%) of the pancreas, and less frequently in the body (n=6, 16%). Previous studies have reported a more equal distribution of the tumors between the 3 different parts of the pancreas [6,17,24,25].

The clinical manifestations of insulinoma may be nonspecific. Interestingly, 3 of our 41 (7%) patients had falsely been diagnosed with epilepsy before they were diagnosed with insulinoma. In fact, diagnostic delay still remains a concern for many patients with insulinoma. In earlier reports, the mean duration of symptoms prior to diagnosis of an insulinoma has been between 15 months and 3.8 years [6,17,28,29]. In the current study, the median duration of symptoms prior to insulinoma diagnosis was much shorter (7 months) and the median time from first physician's visit to correct diagnosis was only 39 days.

A spontaneous hypoglycemic episode was very common among our patients, and only 1 patient was diagnosed with insulinoma in connection with a detection of an incidentally discovered pancreatic lesion. Nevertheless, a 72-h fasting test was conducted in 28 (76%) of the patients to confirm endogenous hyperinsulinism. The mean P-glucose and median S-insulin and C-peptide at diagnosis (spontaneous or during fasting test) were within similar ranges as in previous studies [25,26,28,30]. In a study from the Mayo Clinic (1999-2007) the sensitivity of P-glucose ≤3 mmol/L at the end of a fasting test was <60%, 93% for S-insulin ≥6 μU/mL and 100% for C-peptide ≥0.2 nmol/L. If the same diagnostic criteria had been applied in our study, the sensitivity of P-glucose, S-insulin, and C-peptide, as measured in our center, would have been 93%, 100%, and 97%, respectively, supporting the current diagnostic criteria for endogenous hyperinsulinism

test [31]. Interestingly, however, 1 patient ultimately diagnosed with insulinoma did not develop neuroglycopenic symptoms after 72 h of fasting. The lowest P-glucose was 3.1 mmol/L and the lowest C-peptide (0.18 nmol/L) was below the diagnostic threshold of <0.2 nmol/L. At the termination of the test S-insulin was only moderately elevated (5.7 μU/mL). Also, it is interesting that the diagnostic delay in this patient was estimated to be 9 years; moreover, the patient had falsely been diagnosed with epilepsy.

Six of the 37 (16%) patients in our cohort had metastatic insulinoma, comparable to 3 other reports [3,17,32] but somewhat higher than in others [4,6,24,26-28,33]. In agreement with previous reports [25,34], 2- to 3-fold higher S-insulin and C-peptide concentrations were observed in patients with malignant insulinoma compared to benign tumor. As in numerous other reports, all insulinomas included in our study were singular and of solid character [6,17,25,26,29,35]. However, also in agreement with previous studies [27,36], malignant insulinomas were larger and had a higher Ki-67 index compared to benign tumors.

It has been reported that the rate of successful preoperative identification of insulinomas by noninvasive modalities remains around 75% [26], and that CT with contrast is the most frequently used initial noninvasive technique to locate insulinomas [37]. In the current study, the sensitivity of CT was 78%. The reported sensitivity of CT ranges from 30-66% [35]. In 2 more recent studies from 2011 and 2017, the sensitivity of CT was 68% and 62%, respectively [25]. Regarding EUS, we recorded a sensitivity of 100% in detecting insulinoma. Admittedly, this number is high, but still comparable to previous publications that reported a high sensitivity of EUS, somewhere in the range of 90-95% [25,38,32]. Importantly, some authors suggest a significantly lower sensitivity of EUS regarding tumors located in the pancreatic tail (<50%) [39,40], which was obviously not the case in the current study. Thus, based on the presented results, we argue that EUS is superior to CT scan in the detection of insulinoma, also in a modern cohort of patients. Other imaging modalities were used more sporadically in our cohort. It is, however, interesting that Ga68-DOTATATE-PET revealed a tumor in all 5 patients investigated with this method. In fact, a recent meta-analysis of noninvasive modalities for detection of insulinoma demonstrated that PET/CT had a significantly better diagnostic performance than both CT and magnetic resonance imaging [41].

A major strength of the current study is that all patients with a suspected insulinoma in the VGR are referred to the department of endocrinology at the Sahlgrenska University Hospital for evaluation and management, and that the DRG-registry, which was used to identify the insulinoma patients, is reliable, since it covers all patients managed by all relevant healthcare units in West Sweden. Hence, we are quite confident that all patients diagnosed with insulinoma during the study's timeframe were correctly identified and included in the study. In addition, the large catchment area covered in the study guarantees a significant study population and permits adequate comparison of the recorded results, both with historical Swedish cohorts and with contemporary international studies.

Admittedly, the study also had limitations. The rarity of insulinoma itself leads to a risk of underestimation of the true incidence in all similar studies. Overlooking a few cases automatically reduces the incidence. Regarding the duration of symptoms before diagnosis there is always a risk of a recall bias, which might affect the results. Regarding the diagnostic imaging of insulinoma, there is continuous technical development of both hardware and software, which might affect the sensitivity of various imaging modalities over time. However, it would be impossible to compare different methods without an adequate number of patients, which in turns requires a sufficiently long study timeframe.

In conclusion, the presented data suggest that the incidence of insulinoma is not increasing, but instead seems to be stable compared with data from the late 1980s and 1990s. Hopefully, an increased awareness of insulinoma and its symptoms among physicians explain a shorter doctor´s delay as compared with old studies. Finally, and if available, EUS can be recommended as part of the workup in the detection of insulinomas.

Summary Box

What is already known:

- Insulinoma is a rare pancreatic neuroendocrine neoplasm and relevant epidemiological studies are scarce
- An increasing incidence of insulinoma has recently been suggested
- There is a lack of data on the sensitivity of insulinoma detection comparing computed tomography (CT) and endoscopic ultrasound (EUS)

What the new findings are:

- Insulinoma remains a rare tumor in the modern era, with a mean annual incidence of 1.3 cases per million/year
- The annual incidence in the current study is compatible with the reported incidence in Sweden during the 1980s, i.e., remaining stable over the years
- Preoperative CT and EUS detected an insulinoma in 28/36 (78%) and 21/21 (100%) cases, respectively, illustrating the superiority of EUS as a noninvasive imaging modality

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