Secular Trends in the Presentation and Management of Functioning Insulinoma at the Mayo Clinic, 1987–2007

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Objective: The objective of the study was to assess changes in the presentation and diagnostic and radiological evaluation of patients with surgically confirmed insulinoma at the Mayo Clinic 1987–2007.

Methods: A retrospective analysis of patients with insulinoma was conducted. Patients with prior gastric bypass were excluded.

Results: A total of 237 patients [135 women (57%)] were identified. Hypoglycemia was reported solely in the fasting state in 73%, the fasting and postprandial state in 21%, and exclusively postprandially in 6%. There was a predominance of men in the postprandial symptom group. Considering the period of study by quartile, outpatient evaluation increased from 35 to 83% and successful preoperative localization improved from 74 to 100% comparing the first to the fourth quartiles. Although the rates of localization by noninvasive techniques remained static at approximately 75%, the addition of invasive modalities has resulted in successful preoperative localization in all patients in the past 10 yr. The sensitivity and specificity of the established diagnostic criteria using insulin, C-peptide, proinsulin, β-hydroxybutyrate, and glucose response to iv glucagon were greater than 90% and greater than 70%, respectively.

Conclusions: Although fasting hypoglycemia is characteristic of patients with insulinoma, postprandial symptoms have been reported with increasing, albeit low, frequency. Trends in the evaluation and preoperative management include a shift to outpatient diagnostic testing, an emphasis on successful preoperative localization to avoid blind pancreatic exploration, and a validation of the diagnostic criteria for hyperinsulinemic hypoglycemia. **(*J Clin Endocrinol Metab* 94: 1069–1073, 2009)**

Documentation of Whipple's triad (*i.e.* symptoms of neuroglycopenia that occur at the time of low blood glucose, which resolve when the low blood glucose is corrected) is essential to the diagnosis of a hypoglycemic disorder (1). Insulinomas are relatively rare islet cell tumors characterized classically by the presence of hypoglycemia in the fasting state. After excluding factitial hypoglycemia, insulinomas are the most common cause of hypoglycemia in patients who are otherwise well and have no systemic illnesses (2). Evolving clinical experience with insulinomas led to the development of the 72-h fast (3) as the test of choice for the documentation of Whipple's triad and determination of the etiology (insulin mediated *vs.* noninsulin mediated) of the hypoglycemia (2).

Scattered case reports (4–7) have led to an increasing awareness of patients with functioning insulinoma in whom hypoglycemia occurs in the postprandial period. The prevalence of post-

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Abbreviations: BOHB, β-Hydroxybutyrate; CT, computed tomography; EUS, endoscopic ultrasonography; F, fasting state; MEN-1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; PC, postprandial state; SACST, selective arterial calcium stimulation test; US, ultrasound.

prandial hypoglycemic symptoms experienced by patients with insulinoma has not been reported. The current health care environment has created financial and logistical pressures that impede the ease with which the 72-h fast can be performed. In addition, the relatively recent availability of invasive testing for localization/regionalization purposes such as endoscopic ultrasonography (EUS) (8) and the selective arterial calcium stimulation test (SACST) (9) should theoretically decrease the frequency to which blind pancreatic exploration for insulinoma is resorted.

Awareness of these potential changes in the classical clinical presentation and management of patients with functioning insulinoma has led to the present effort to quantify trends, if any, and furthermore assess the accuracy of the diagnostic criteria generated at this institution for endogenous hyperinsulinemic hypoglycemia (2, 10). Therefore, a retrospective analysis of a cohort of patients with functioning insulinoma treated at the Mayo Clinic from 1987 through 2007 was undertaken. This period was selected for its substantial duration and number of patients involved as well as lack of overlap with the last review of insulinoma from this institution, which covered the period 1927–1986 (11).

Patients and Methods

With approval of the Institutional Review Board of the Mayo Foundation, data acquisition from the comprehensive unitary Mayo Clinic medical record system was conducted on consecutive patients with surgically confirmed insulinoma diagnosed and operated on at the Mayo Clinic. However, patients with insulinoma and a prior history of gastric bypass were excluded because of the potential impact of the bariatric surgery on the timing of symptoms. In the rare instance (n = 3) of a second operation for recurrent insulinoma during this period of study, the data obtained with the first surgical procedure were used in the analysis. Determination of the timing of symptoms of hypoglycemia with respect to meals or food deprivation was based on each patient's self-report. Although patient interviews in this cohort were, of necessity, conducted by several physicians in the Division of Endocrinology, the bulk of the histories were obtained by one author (F.J.S.).

An inpatient evaluation was defined by the documentation of Whipple's triad during a 72-h fast as an inpatient, regardless of whether the fast was initiated as an outpatient or inpatient. Outpatient evaluation was defined as the satisfaction of Whipple's triad during a spontaneous episode of hypoglycemia in the outpatient setting or a positive result during an outpatient fast or mixed-meal test.

Outpatient evaluations were conducted in the endocrine testing center located in the clinic in which the supervising endocrinologist is on site and readily available. Blood is drawn for a hypoglycemia survey [serum glucose, insulin, C-peptide, proinsulin, β-hydroxybutyrate (BHOB), and sulfonylurea screen] when a patient experiences symptoms. A formal outpatient fast begins with the last meal at 1900 h the night before or at a later time as guided by the patient's history. Assuming that the patient is accompanied by a family member, the outpatient fast can be conducted safely. If the fast is not positive within 22 h (assuming a 1900 h start), the fast is continued as an inpatient.

Only patients whose entire diagnostic evaluation was completed at the Mayo Clinic were included in the portion of the analysis addressing symptom timing; patients whose data were obtained from a referring physician and judged to be adequate for the diagnosis of functioning insulinoma were excluded from this section of the analysis. To characterize the timing of patients' self-reported hypoglycemia symptoms, postprandial symptoms were defined as those occurring within 4 h of meal ingestion and fasting symptoms as those occurring more than 4 h after the last food intake. Three patients with serendipitously discovered hypoglycemia who were asymptomatic during ordinary life activities but symptomatic during 72-h fasts and 20 patients in whom cognitive or other language difficulties impaired accurate establishment of symptom timing were excluded.

Tumor localization procedures were characterized as noninvasive in the case of transabdominal ultrasound (US) and triple-phase spiral computed tomography (CT) of the pancreas and, in a few cases, magnetic resonance imaging (MRI). Localization/regionalization procedures were characterized as invasive if EUS and SACST were used. A negative result for a given category (invasive *vs.* noninvasive) was defined as a lack of identification of insulinoma by each modality used in that category. A positive result was defined as identification of the tumor or its region of the pancreas by at least one modality in a given category. For patients with multiple pancreatic masses, a study was considered positive if at least one of the masses was identified. Blind pancreatic exploration was defined as pancreatic exploration in the absence of a positive result for any localization procedure conducted before operation.

To determine the accuracy of current diagnostic criteria for endogenous hyperinsulinemic hypoglycemia (2, 10), the cohort of patients evaluated subsequent to the establishment of those criteria (1999–2007) were studied. Assessment of sensitivity and specificity was conducted on those patients with insulinoma who had complete data sets [*i.e.* insulin, C-peptide (12), proinsulin (13), BHOB, and plasma glucose response to iv glucagon (14)], obtained at the time of hypoglycemia). In addition, 20 subjects with failed confirmation of Whipple's triad during 72-h fasts, and complete data sets with terminal plasma glucose concentrations 60 mg/dl or less, were considered as normal subjects.

The trends in the presentation, evaluation, and management of functioning insulinoma were evaluated by dividing the period of study (1987–2007) into quartiles (1987–1992, 1993–1997, 1998–2002, and 2002–2007).

Results

Patient characteristics

The cohort of functioning insulinomas consisted of 237 patients (135 women, 57%), aged 50, 17–86 yr (median, range) with a body mass index of 27.8, 17.5–53.8 kg/m^2 and 1, 1–14 tumors per patient. Malignant tumors occurred in 10 patients (4%).

There were 14 patients (6%) with multiple endocrine neoplasia type 1 (MEN-1) syndrome, 11 of whom had a prior diagnosis of MEN-1 and three who were recognized on the basis of additional endocrinopathy identified concurrent with the diagnosis of insulinoma. Ten of the MEN-1 patients (71%) were men and 13 (93%) had benign insulinomas. Multiple tumors were a characteristic of the previously diagnosed MEN-1 group; two patients with concurrent additional endocrinopathy (-ies) had solitary insulinomas. Seven patients (3%) without MEN-1 had multiple tumors (two, two to 11), five of whom were women (71%).

Symptom timing

Among the 214 patients who provided a reliable history, symptoms of hypoglycemia were reported to occur exclusively in the fasting state (F) in 157 (73%), postprandial state (PC) in 13 (6%), and both fasting and postprandial state (PC+F) in 44 (21%) (Fig. 1).

Among the 13 patients who reported exclusively postprandial symptoms of hypoglycemia, eight patients had biochemical confirmation with either mixed-meal testing or laboratory blood

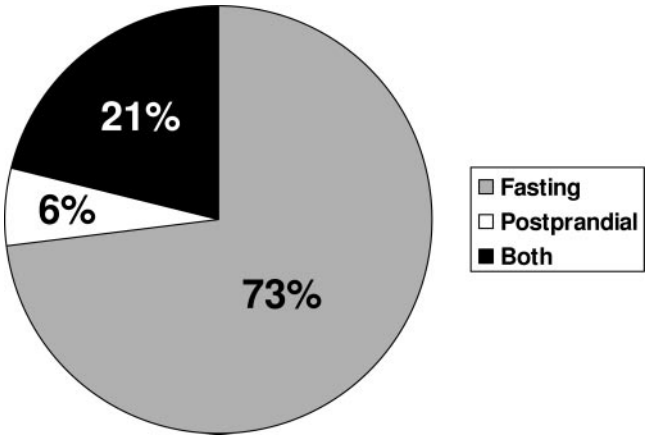

FIG. 1. Distribution of the timing of hypoglycemia symptoms in 214 patients with functioning insulinoma.

values drawn at the time of spontaneous symptoms in the postprandial state. Seventy-two-hour fasts conducted in three of these eight patients were negative. The remaining five patients had positive 72-h fasts.

Except for a slight predominance of men in the group with exclusively postprandial symptoms (PC 54% *vs.* F 42.% *vs.* PC+F 43.%), age, body mass index, number of insulinomas, and the presence of benign or malignant insulinoma did not differ among the groups. When the period of study was considered by quartile, there was an increase in the frequency of exclusively postprandial symptoms from 2% in the first quartile (1987–1992) to 10% in the last quartile (2003–2007). There was no histological evidence for nesidioblastosis in any patient with postprandial symptoms, exclusively or in combination with fasting symptoms, which might have contributed to the timing of symptoms.

Site of evaluation: outpatient *vs.* inpatient evaluation

Over the period of study, the frequency with which diagnostic data obtained by the referring physician was judged to be adequate, and therefore not repeated, remained relatively unchanged at less than 15% of patients. There was a notable increase in outpatient assessment with a reciprocal decrease in inpatient evaluation when the first decade was compared with the second decade of study (Table 1). In the first two quartiles (1987–1992, 1993–1997), an average of 34% of patients underwent evaluation for functioning insulinoma as an outpatient, whereas in the most recent quartile (2003–2007), 83% of patients had outpatient assessments.

TABLE 1. Inpatient *vs.* outpatient evaluation by quartile of study period

Quartile	1987–1992, n (%)	1993–1997, n (%)	1998–2002, n (%)	2003–2007, n (%)
n	54	52	62	69
Inpatient	33 (61)	32 (62)	15 (24)	10 (15)
Outpatient	18 (33)	15 (28)	40 (65)	50 (72)
Outside data	3 (6)	5 (10)	7 (11)	9 (13)

Rates of blind pancreatic exploration

All patients underwent noninvasive localization with transabdominal ultrasound and/or triple-phase spiral CT of the pancreas. Rarely MRI was used. The rates of detection of the insulinomas by at least one of these modalities remained constant over the period of study at 74, 71, 77, and 80% for the first through fourth quartiles, respectively (Table 2). Considering all quartiles of study, CT scan had an accuracy rate of 55%, US of 61%, and MRI of 42% for the detection of functioning insulinomas.

Invasive localization procedures using EUS and/or SACST were not available during the first quartile (1987–1992). Subsequently they were used in 21, 39, and 38% of patients for quartiles 2-4, respectively. Overall, EUS had a sensitivity of 75% and SACST of 93% for the localization or regionalization of functioning insulinomas.

Invasive procedures were conducted in some patients despite positive noninvasive results for a variety of reasons, including better delineation of the relationship of the insulinoma to the pancreatic duct (EUS), confirmation that the observed lesion (especially in patients with postprandial symptoms) was indeed functional (SACST), and for the potential identification (EUS) of additional islet cell tumors in MEN-1 patients. The additional contribution to the preoperative localization of insulinoma from invasive studies was 8, 21, and 20% for quartiles 2-4, respectively. The resulting rates of blind pancreatic exploration per quartile of study were 26, 21, 2, and 0%, respectively. No blind pancreatic exploration has been undertaken at this institution since 1998.

Sensitivity and specificity of diagnostic evaluation

Among the patients with insulinoma who underwent diagnostic evaluation at the Mayo Clinic during the period 1999–2007, 69 patients had complete sets of diagnostic parameters, namely glucose, insulin, C-peptide, proinsulin, BHOB, and plasma glucose response to 1 mg glucagon iv. In addition, 20 patients without a hypoglycemic disorder had complete data sets and plasma glucose less than 60 mg/dl at the end of 72-h fasts and were therefore considered as normal controls. The sensitivity and specificity of the established diagnostic parameters were insulin ($\geq$3 μU/ml), 93 and 95%; C-peptide ($\geq$0.6 ng/ml), 100 and 60%; proinsulin ($\geq$5 pmol/liter), 100 and 68%; BHOB ($\leq$2.7 mmol/liter), 100 and 100%; and plasma glucose response to iv glucagon ($\geq$25 mg/dl), 91 and 95%, respectively. The specificity of these parameters was improved when compared with normal patients whose plasma glucose at the end of a prolonged fast was 50 mg/dl or less: insulin, 100%; C-peptide, 78%; proinsulin, 78%; and glucose response to glucagon, 100% (Table 3).

Discussion

Buttressed by scattered case reports (3–6), the appreciation that patients with functioning insulinoma may report hypoglycemic symptoms in the postprandial state has grown over time and is confirmed by this retrospective analysis of a large cohort of patients. It was not the intent of this study to confirm the accuracy

TABLE 2. Localization procedures

Quartile	1987–1992	1993–1997	1998–2002	2003–2007
Noninvasive localization studies				
n	54	52	62	69
Percent done	100	100	100	100
Percent positive	74	71	77	80
Invasive localization studies				
n	0	11	24	26
Percent done	0	21	39	38
Percent additional positive	0	8	21	20
Percent blind pancreatic exploration	26	21	2	0

of the anamneses by comprehensive testing but to report what was proffered by the patient. Nevertheless, in more than half of the patients who self-reported exclusively postprandial hypoglycemia symptoms, the postprandial hypoglycemia was confirmed biochemically. Three of these patients (8) underwent a 72-h fast with negative results.

These data reinforce the notion that an insulinoma cannot be excluded in patients with postprandial symptoms of hypoglycemia (5). This action would be unwarranted because 6% of patients reported symptoms solely in the postprandial state and 21% of patients reported symptoms in both the postprandial and fasting states. Intriguingly, the only demographic characteristic distinguishing those patients with exclusively postprandial hypoglycemia from those with fasting hypoglycemia was a slight male predominance. Of note is the fact that among the case reports of seven patients with functioning insulinoma and postprandial hypoglycemia, four were men (4–7).

The shift from a reliance on the 72-h fast conducted in an inpatient setting to the confirmation of Whipple's triad in the outpatient setting observed over the past 2 decades is probably a consequence of not only the pressure to minimize hospitalization for financial reasons but also the greater ease with which diagnostic data can be obtained during spontaneous episodes or during an outpatient fast.

The success rate of identifying insulinoma at this institution with noninvasive testing such as CT and transabdominal US has remained constant at approximately 75% over the 2 decades of this study. However, with the implementation of EUS and SACST for patients with negative noninvasive imaging in the period 1998–2007, the rate of blind pancreatic exploration dropped from about 25% to zero. In selected instances invasive studies were undertaken to aid preoperative planning and patient counseling as well as exclude the presence of other functioning tumors or confirm that the visualized lesion(s) was (were) indeed functional. The effect of this additional invasive testing on surgical morbidity and patient satisfaction are difficult to quantify and beyond the scope of this review. The number of patients requiring reoperation was extremely small and occurred in the first decade of the study. It remains uncertain whether the availability of EUS and SACST will completely eliminate the necessity for re-operation.

TABLE 3. Sensitivity and specificity of diagnostic parameters for insulinoma (n = 69) *vs.* subjects with a normal fast (n = 20)

	Sensitivity (%)	Specificity (%)	
End of fast glucose (mg/dl)	<60	<60	≤ 50
	n = 69	n = 22	n = 10
Median, range	40, 20–58	52, 37–55	45, 37–49
Parameter			
Insulin (≥3 μU/ml)	93	95	100
C-peptide (≥0.6 ng/ml)	100	60	78
Proinsulin (≥5 pmol/liter)	100	68	78
BHOB (≤2.7 mmol/liter)	100	100	100
δ-G (≥25 mg/dl)[a]	91	95	100

[a] Plasma glucose response to 1 mg iv glucagon. G, Glucose.

This retrospective review also provided the opportunity to examine the accuracy of diagnostic criteria for endogenous hyperinsulinemic hypoglycemia generated in the late 1990s at this institution (2, 10, 12–14). These criteria have been used as complementary phenomena without expectation that the results from each measurement would be congruent with the others 100% of the time. Examination of the sensitivity and specificity of each parameter in patients with and without insulinoma permitted an assessment of the strength of accuracy of each parameter alone as well as in comparison with each other. The well-recognized phenomenon (15) of glucose values less than 50 mg/dl in otherwise healthy women at the termination of a 72-h fast provided a cadre of healthy subjects for the calculation of specificity. All 20 of the normal subjects were women. We are unaware of any evidence to suggest that the specificity data generated from this gender would not apply to men.

We observed a high degree of sensitivity (>90%) for each parameter and similar high degrees of specificity for insulin, BOHB, and the glucose response to iv glucagon. The lower specificities of C-peptide and proinsulin were improved when the ambient plasma glucose was 50 mg/dl or less in the control subjects. Fortunately, the likelihood of a false-positive diagnosis of insulinoma based solely on C-peptide or proinsulin is remote when considered in light of the normal values for the other parameters and the lack of significant symptomatology attributable to neuroglycopenia.

In conclusion, over the past 20 yr, patients with functioning insulinoma have been reporting postprandial symptoms of hypoglycemia with increasing, albeit low, frequency have undergone a shift to successful evaluation (~80%) in the outpatient setting and have avoided blind pancreatic exploration as a result of modern localization strategies. Furthermore, the established criteria for endogenous hyperinsulinemic hypoglycemia have been shown to have high degrees of sensitivity and specificity.

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References

1. **Whipple AO** 1938 The surgical therapy of hyperinsulinism. J Int Chir 3:237–276
2. **Service FJ** 1999 Diagnostic approach to adults with hypoglycemic disorders. Endocrinol Metab Clin North Am 28:519–532, vi
3. **Skillern PG, Rynearson EH** 1953 Medical aspects of hypoglycemia. J Clin Endocrinol Metab 13:587–603
4. **Connor H, Scarpello JH** 1979 An insulinoma presenting with reactive hypoglycaemia. Postgrad Med J 55:735–738
5. **Jordan RM, Kammer H** 1976 An insulinoma without fasting hypoglycemia. Am J Med Sci 272:205–209
6. **Kar P, Price P, Sawers S, Bhattacharya S, Reznek RH, Grossman AB** 2006 Insulinomas may present with normoglycemia after prolonged fasting but glucose-stimulated hypoglycemia. J Clin Endocrinol Metab 91:4733–4736
7. **Wiesli P, Schmid C, Perren A, Pfammatter T, Spinas GA, Keller U** 2004 Hypoglycemia in response to glucose and glucagon in insulinoma patients with a negative prolonged fast: functional and morphological properties. J Endocrinol Invest 27:832–838
8. **Glover JR, Shorvon PJ, Lees WR** 1992 Endoscopic ultrasound for localisation of islet cell tumours. Gut 33:108–110
9. **Doppman JL, Miller DL, Chang R, Shawker TH, Gorden P, Norton JA** 1991 Insulinomas: localization with selective intraarterial injection of calcium. Radiology 178:237–241
10. **Service FJ** 1995 Hypoglycemic disorders. N Engl J Med 332:1144–1152
11. **Service FJ, McMahon MM, O'Brien PC, Ballard DJ** 1991 Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. Mayo Clin Proc 66:711–719
12. **Service FJ, O'Brien PC, McMahon MM, Kao PC** 1993 C-peptide during the prolonged fast in insulinoma. J Clin Endocrinol Metab 76:655–659
13. **Kao PC, Taylor RL, Service FJ** 1994 Proinsulin by immunochemiluminometric assay for the diagnosis of insulinoma. J Clin Endocrinol Metab 78:1048–1051
14. **O'Brien T, O'Brien PC, Service FJ** 1993 Insulin surrogates in insulinoma. J Clin Endocrinol Metab 77:448–451
15. **Merimee TJ, Fineberg SE** 1973 Homeostasis during fasting. II. Hormone substrate differences between men and women. J Clin Endocrinol Metab 37:698–702