INSULINOMAS

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ABSTRACT

Insulinomas are rare pancreatic tumors (incidence of 0.4 per 100,000 person yrs. or 4 cases per million per year. Most are solitary and benign. Multiple tumors occur in MEN-1. Malignancy is more frequent in MEN-1 than sporadic. The diagnosis requires demonstration of inappropriately high insulin for the prevailing blood glucose in a 72h fast. A high proinsulin: insulin ratio indicates malignancy. Localization of the tumor by transabdominal ultrasound and computed tomography is the preferred initial option followed by endoscopic ultrasonography or arterial stimulation with hepatic venous sampling. For single solitary tumors excision is the treatment of choice. With multiple tumors we recommended that venous sampling regionalizes the origin of the insulin and directs the region for resection. With suggestion of malignancy e.g. elevated Pancreastatin, NKA, and Proinsulin/insulin ratio of >0.8 we recommend debulking of the pancreatic tumors, surrounding lymph nodes. If hyperinsulinemia and hypoglycemia persist diazoxide with a thiazide diuretic relieves hypoglycemia. Liver metastases can be resected, or treated by bland or chemo-embolization, radiofrequency and cryoablation depending on availability at the institution. In patients with unresectable metastatic tumors we prefer Lanreotide which is approved for control of tumor growth and if necessary peptide receptor radiotherapy (PRRT) with an option to utilize temodar and xeloda. For intractable hypoglycemia with gastric bypass programmed pumps containing glucagon have shown promise.

INTRODUCTION

Insulinomas are rare and often benign gastroenteropancreatic neuroendocrine tumors. The hallmark features of fasting hypoglycemia include neuroglycopenic (e.g. confusion, visual changes, unusual behavior) and sympathoadrenal (e.g. palpitations, diaphoresis, tremulousness) symptoms. A firmly established diagnosis of an insulin-secreting lesion of the pancreas is essential for successful management. Therefore, it is critically important to rule out other causes of hypoglycemia associated with fasting (1). A detailed differential diagnosis may be found in Table 1.

Table 1. Classification of Hypoglycemia

Fasting Hypoglycemia • Hyperinsulinemia – Islet cell adenoma, carcinoma, hyperplasia, nesidioblastosis • Autoimmune with insulin/insulin receptor antibodies • Counter regulatory hormone deficiency • Gastric bypass surgery associated hypoglycemic syndrome (Non-insulinoma pancreatogenous hypoglycemia • Anterior pituitary insufficiency-GH, ACTH • Adrenocortical insufficiency • Hypothyroidism (severe) • Impaired hepatic function • Large non-islet tumor • Hepatocellular insufficiency • Ethanol/malnutrition • Sepsis • Specific enzymatic defects (childhood) • Impaired renal function • Substrate deficiency • Fanconi syndrome (renal loss of glucose) • Nursing • Severe inanition • Severe exercise
Drug induced reactive hypoglycemia alimentary • "Pre-diabetes" • Endocrine • Idiopathic
Factitious • Surreptitious insulin administration • Surreptitious sulfonylurea administration
Leukemoid reaction • Polycythemia
ACTH = corticotropin; GH – growth hormone

An accurate diagnosis of organic hyperinsulinism can be established with certainty in nearly all cases (1). The specific cause of hyperinsulinism (see Table 1) usually can be determined before exploration. Non-islet cell neoplasms associated with hypoglycemia are given in Table 2.
There is a clinical entity referred to as autoimmune hypoglycemic disease syndrome (also referred to as insulin autoimmune hypoglycemia, or autoimmune hypoglycemia) in which hypoglycemia occurs in the setting of an autoimmune disorder (e.g., Graves' disease, rheumatoid arthritis, lupus). Antibodies to insulin occur in the presence of other autoimmune disease and insulin levels may be normal or high, but C-peptide levels are low. The syndrome may be precipitated in some patients by exposure to drugs containing sulfhydryl groups that react with sulfhydryl groups on insulin and render it immunogenic. The disorder is more

common in Asians. Glucose tolerance testing reveals that plasma glucose is elevated early and reduced late because of the buffering effect of antibodies on the action of secreted insulin. Disassociation of insulin from the antibodies can lead to hypoglycemia. The disease usually is self-limited as titers fall with time, leading to remission, although corticosteroids have been used.

A second form of autoimmune mediated hypoglycemia is the insulin B resistance syndrome. Type B insulin-resistance syndrome, is characterized by the presence of autoantibodies directed to the cell-surface insulin receptor (2). Only a small minority of patients with type B insulin-resistance syndrome experience hypoglycemic manifestations; most of them present with severe hyperglycemia associated with extreme insulin resistance (3). A common feature of type B insulin-resistance syndrome is the co-occurrence of autoimmune disorders, such as systemic lupus erythematosus (SLE) (3). Anti-insulin receptor antibodies impair the binding of insulin to its receptor and cause insulin resistance and most commonly hyperglycemia because of the insulin receptor-antagonizing action of the autoantibodies (3). Less commonly, anti-insulin receptor antibodies may have agonist activity, resulting in hypoglycemia. This phenomenon appears to be caused by the binding of autoantibodies to insulin receptors, which inhibits the degradation of insulin and results in hyperinsulinemia, followed by subsequent hypoglycemia. Lupsa et al. (4) who followed 34 patients with type B insulin-resistance syndrome who were admitted to the Clinical Research Center of the National Institutes of Health between January 1973 and July 2008 reported that 24% (8/34) manifested some form of hypoglycemia during the course of the illness. Hypoglycemia may occur during the fasting or postprandial states, usually after a preceding period of hyperglycemia. A few patients with type B insulin-resistance syndrome may initially present with spontaneous hypoglycemia and never manifest hyperglycemia (4).

Management is as for other autoimmune diseases and use of steroids, immunosuppressive agents and IV immunoglobulin have all been tried with some success. Insulin antibodies can be detected in blood and in the B syndrome insulin levels are very high despite resistance to the action of insulin.

With the increasing popularity of gastric bypass surgery for morbid obesity, physicians caring for these patients need to be aware of associated hypoglycemic syndromes**.** Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) is a recently recognized syndrome occurring in adults who have had gastric bypass (5). Initially described in adults as sporadic cases, Service et al at the Mayo Clinic in Rochester, Minnesota described NIPHS developing about 1-3 years after a roux-en-Y gastric bypass, presenting with neuroglycopenic symptoms about 1-3 hours postprandial. Pancreatic specimens with NIPHS have shown beta cell hypertrophy, increased islet cell size with hyperchromatic nuclei and increased periductular islet cells, findings characteristic of nesidioblastosis seen in neonates and infants with persistent hyperinsulinemic hypoglycemia (6). Fasting studies for insulinoma and imaging studies are negative for identifying a source of hypoglycemia. Selective arterial calcium stimulation testing are of uncertain significance in the setting of NIPHS, often showing elevated insulin levels in more than one arterial distribution, usually the splenic artery (tail and body of pancreas) and

superior mesenteric artery (uncinate process) distributions, and less often the gastroduodenal artery (head) distribution (5),(7). Most cases have been successfully treated with gradient guided distal pancreatectomy up to the level of the superior mesenteric vein even when calcium stimulation studies have shown elevated insulin levels predominantly in the gastroduodenal or superior mesenteric artery distribution. Patients can be medically managed primarily, or for recurrent symptoms, with diazoxide (8). We have successfully used a low carbohydrate diet with multiple small feeding of meals containing < 15g of refined carbohydrate. Success cam also occur with the use of Acarbose which reduces the glycemic burden and the reactive hypoglycemic burden and in difficult cases we have resorted to Rapamycin in low dose which suppress (9). The etiology of NIPHS after roux-en-Y gastric bypass is unknown. Proposals include bypass of the proximal intestine, secretion of GLP-1 or decreased ghrelin, or hyperinsulinemia with rapid weight loss. Suggestions that it may arise from an exaggerated GLP-1 response to meals with stimulation of islet neogenesis has not stood up to careful scrutiny of gastric bypass patients.

DIAGNOSIS

The cardinal features of insulinomas are indicated in table 2.

Table 2. The cardinal features of insulinomas

Whipples triad

- Symptoms of hypoglycemia
- Low blood glucose relieved by ingestion of glucose
- Benign 90%

Rule of 10s

- 10% malignant
- 10% ectopic
- 10% MEN syndrome
- Nesidioblastosis rare in adults, more common now with gastric bypass (NIHPPS)

The principal feature of an insulinoma is hypoglycemia but there are other malignancies which can cause hypoglycemia as well as nesideoblastosis. The clinical presentation, syndrome, tumor types, their sites and the hormone production are shown in table 3.

Table 3. Features of hypoglycemic tumors and nesedioblastosis

Clinical Presentation	Syndrome	Tumor Type	Sites	Hormones
Hypoglycemia	Whipple's triad	Insulinoma, sarcoma, hepatoma, nesideoblastosis	Pancreas, retroperitoneal liver	Insulin, IGF1, IGF11

While hypoglycemia is a hallmark of insulinoma, the blood glucose level alone is not diagnostic of insulinoma, nor in general is the absolute insulin level elevated in all cases of organic hyperinsulinism. Hypoglycemia activates the adrenergic and cholinergic nervous systems and depending on the degree of the hypoglycemia presents different levels of impairment of neurologic function (Table 4).

Table 4. Distinguishing signs and symptoms of insulinomas

Neurogenic (10) (11)	Neuroglycopenic (10) (11)
• Adrenergic Palpitations Tremor Anxiety/arousal/nervousness • Cholinergic Sweating/diaphoresis Hunger Paresthesiae Circumpolar tingling	• Blurred Vision • Cognitive impairments • Behavioral changes • Psychomotor abnormalities • Confusion • Disorientation • Memory Loss • Seizure • Stupor

Factors affecting glycemic thresholds are poorly controlled type 1 and type 2 diabetes tight glycemic control in type 1 diabetes, and older age (11) (12).

The standard test remains a 72-hour fast while the patient is closely observed; (13). The rate of decline in glucose has not warranted the use of a glucometer. More than 95% of cases can be diagnosed based on responses to a 72-hour fast. Serial glucose and insulin levels are obtained over the 72 hours until the patient becomes symptomatic. Because the absolute insulin level is not elevated in all patients with insulinomas, a normal level does not rule out the disease. However, a fasting insulin level of greater than 24 μU/mL is found in approximately 50% of patients with insulinoma. Values of insulin greater than 7 μU/mL after a more prolonged fast in the presence of a blood glucose less than 40 mg/dL also are highly suggestive. A refinement in the interpretation of glucose and insulin levels has been established by determining the ratio of insulin levels (mU/mL) to the concomitant glucose level (mg/dL). An insulin/glucose ratio of greater than 0.3 has been found in virtually all patients proven to have an insulinoma or other

islet cell disease causing organic hyperinsulinism. The accuracy of the test can be increased by calculating the amended insulin/glucose ratio as follows:

amended ratio = [insulin (mU/mL) x 100]/[glucose (mg/dL) - 30] Normal <50.

If the value is greater than 50, then organic hyperinsulinism is certain (1). Table 5 outlines the diagnostic testing for an insulinoma.

Table 5. Diagnostic Testing for an insulinoma

▪ Blood glucose levels alone not diagnostic, not all patient have elevated insulin levels ▪ Best test is still a 72h fast with glucose and insulin/C peptide levels q4h ▪ Fasting insulin >24uU/ml in 50% ▪ Insulin levels >7uU/ml with glucose <40 mg/dl nearly all	▪ Insulin/glucose mg/dl >0.3 certain ▪ Amended ratio = insulin uU/ml/glucose mg/dl 30, >50 ▪ Proinsulin/insulin ratio >24 in 90% insulinomas and if >40 suggests malignancy ▪ High insulin and low C peptide = factitious insulin administration ▪ Insulin response to secretin (2U/kg IV) peak response in 5 minutes. Single adenomas (17 uU/ml) and nesideoblastosis (10 uU/ml) no response multiple adenomas and hyperplasia have excessive response (>2 – 400uU/ml)

Measurements of proinsulin and C peptide also have proven to be valuable in patients suspected of having organic hypoglycemia (14). Normally, the circulating proinsulin concentration accounts for less than 22% of the insulin immunoreactivity but is greater than 24% in over 90% of individuals with insulinomas. Furthermore, when the proinsulin level is greater than 40%, a malignant islet cell tumor should be strongly suspected (1) (15) (16). The C-peptide level is useful in ruling out factitious hypoglycemia from self-administration of insulin. Commercial insulin preparations do not contain C peptide and low C-peptide levels combined with high insulin levels confirm the diagnosis of self-administration of insulin. Patients who take sulfonylureas surreptitiously may have raised insulin and C-peptide values soon after ingestion, but chronic use will result in hypoglycemia without raised insulin or C-peptide levels. Only a high index of suspicion and measurement of urine sulfonylureas will lead to the correct diagnosis. The insulin response to secretin stimulation (2 U/kg intravenously; peak response in 1-5 minutes) is a valuable measure to differentiate multiple adenomas from nesidioblastosis and single adenomas (17). Patients with single adenomas and nesidioblastosis do not respond to secretin (normal maximal increment $\leq$ 74 mU/mL) whereas those with multiple adenomas or hyperplasia have an excessive insulin response to the administration of secretin (insulin levels of 214 and 497 mU/mL, respectively).

A study in benign and malignant insulinoma showed that somatostatin receptor subtype 4 was most frequently expressed in both benign and malignant tumors (3 of the 6 malignant tumors), but none of the benign tumors expressed somatostatin receptor subtype 5. The other receptor

subtypes were expressed in low numbers with no difference between benign and malignant tumors (18).

LOCALIZATION OF INSULINOMAS

Once the diagnosis of insulinoma is confirmed, every effort should be made to localize the tumor. Preoperative localization is important because approximately 30% of insulinomas are less than 1 cm in diameter and 10% are multiple. In addition, 10 to 15% are malignant and 10% will have either islet cell hyperplasia or nesidioblastosis and no tumor at all (19) (1) (13) (20) (21) (22) (23) (24). Techniques most commonly used to demonstrate tumors in the upper abdomen include contrast enhanced CT and MRI scans of the abdomen, and endoscopic ultrasound (EUS). Each modality has variable reported abilities to identify insulinomas, likely reflecting institutional expertise. Reported sensitivities of identifying insulinomas are 69% - 94.4% for CT, 63% for MRI and 89%-93.5% for EUS (25) (26) (27) (28). EUS is better able to detect lesions in the head of the pancreas (sensitivity 92.6%) as compared to the tail (40%). Until the past decade, the only study considered to be of proven value in the localization of insulinomas was selective pancreatic angiography (13) (22) (29) (30). During this procedure, highly selective injections of contrast, subtraction procedures, and magnification views increase the number of insulinomas identified. In one large series, 90% of insulinomas were reported to be localized by angiography alone (13); however, most groups report less satisfactory results (30). A summary of all reports in the literature found that approximately 60% of insulinomas have been detected by this method (20). Selective intra-arterial injection of calcium with sampling of hepatic vein insulin appears to improve the ability to detect insulinomas, (31) (32) similar to the results seen with intra-arterial secretin in gastrinoma.

Percutaneous trans-hepatic venous sampling (PTHVS) of insulin from pancreatic veins has been used successfully in localizing occult sources of hyperinsulinism (22) (33) (34) (35) (36). We now believe that the combination of a secretin test to determine the nature of the hyperinsulinism (e.g., distinction of hyperplasia from adenoma or multiple adenomatosis) with PTHVS to localize the source provides the best means of establishing the specific cause of organic hyperinsulinism with near certainty. A skilled angiographer and careful analysis of the hormonal data in relationship to the venous anatomy in the individual case are required.
A variety of other imaging methods have been investigated. A recent study suggests that the glucagon-like peptide 1 receptor scan is useful to localize occult insulinomas that cannot be identified by other means (37). A prospective multicenter study from Europe showed that GLP-1 receptor imaging of patients with insulinoma had a positive predictive value of 83% and a higher sensitivity than CT or MRI (38). Multi-modality imaging with specifically designed protocols appears to increase the yield of conventional imaging studies (39). Recently, use of [18F] fluorodopa positron emission tomography has been shown useful for diagnosing and localizing congenital hyperinsulinism in infants (40) and insulinoma or beta cell hyperplasia in adults patients (41). However further study in a larger number of patients as well as comparisons to other non-invasive and invasive imaging studies will be required to more precisely define the utility of these localization methods in patients with hyperinsulinism.

If PTHVS is not available and preoperative localization by angiography or other techniques has been negative, the surgeon may use intraoperative ultrasound if a careful exploration fails to detect a tumor. Some who have used this technique routinely have reported excellent results. Ultrasound does not identify hyperplasia or nesidioblastosis, however, and its sensitivity appears to be operator dependent.

The role of extensive pre-operative localization tests has been questioned. One study showed that intraoperative inspection and palpation localized lesions in 91% and intraoperative ultrasound in 93% of cases. Interestingly, all 5 occult tumors were palpable at surgery. These investigators suggest that PTHVS is helpful in localizing lesions before re-operation, but question the need for extensive pre-operative localization prior to initial exploration in patients believed to have insulinoma (42). On the other hand, another experienced group has shown that since 1994, pre-operative imaging including the use of endoscopic ultrasound was able to identify the tumors 98% of the time. They also found that palpation and intraoperative ultrasound detected 92% of tumors (43).

TREATMENT OF PANCREATIC ISLET β-CELL DISEASE WITH HYPERINSULINISM

The treatment of pancreatic islet β-cell disease usually is surgical; in the great majority of cases, it provides a complete cure. It should be performed only when the diagnosis is certain, however, and only by a surgeon who is skilled in pancreatic surgery. The surgical approach to insulinoma is straightforward when the tumor is localized. Insulinomas are typically removed by enucleation of the tumor and rarely do tumors at the head of the pancreas require a pancreaticoduodenectomy (Whipple procedure). Precise localization obviates blind pancreatic resection (44).

In patients who have been unresponsive to medical therapy and in whom PTHVS or intra-arterial calcium stimulation with venous sampling suggests diffuse or multiple sources, such as adenomatosis, nesideoblastosis, or hyperplasia, a resection of at least 80% of the distal pancreas is indicated after a frozen-section specimen of the pancreatic tail confirms the diagnosis. Recent study confirms the value of intra-arterial calcium stimulation with venous sampling prior (45).

Similar to other types of tumors, there have increasingly been small series and case reports discussing the role of laparoscopy in the management of these tumors. Exploratory laparoscopy and intraoperative ultrasound was able to identify 12 of 14 tumors, and is felt to be equivalent to arteriography with calcium stimulation and venous sampling (46). Laparoscopic enucleating of insulinoma has been shown to be feasible, particularly if the lesion is visualized pre-operatively on CT scan or endoscopic ultrasound (47).

MEDICAL MANAGEMENT OF BENIGN DISEASE

When hypoglycemia can be controlled with diet alone or with small, well-tolerated doses of diazoxide, and/or when the medical condition of the patient increases the hazard of surgery

sufficiently, medical management alone may be considered. Patients with diffuse hyperinsulinism for whom an operation is planned first should have a trial of treatment with diazoxide and a natriuretic benzothiadiazine. Medical treatment is required for the great majority of malignant insulinomas because only occasionally are they cured by operation. Medical treatment for benign insulinomas includes a change in meals to include “lente carbohydrate” or unrefined carbohydrate given as frequently as required to prevent hypoglycemia. Antihormonal therapy may be useful if diet is insufficient. The management of malignant insulinoma is antihormonal and antitumor therapy. As indicated above, the management of NIPHHS syndrome can be quite difficult and several approaches have been taken. Table 6 outlines the approaches to management of NIPHHS Syndrome.

Table 6. Management of Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome

- Somatostatin analogs
- Diazoxide + hyrochlothiazide
- Dilantin
- Acarbose
- mTOR inhibition

Symptoms: Flushing, sweating, palpitations, tingling, confusion, even coma

DIET

The cornerstone of medical management of insulinoma and other forms of hyperinsulinism is the diet. Not uncommonly, patients may avoid symptoms of hypoglycemia for variable periods of time by shortening the number of hours between feedings. For some, the inclusion of a bedtime (11:00 pm) feeding is sufficient; for others, a midmorning, midafternoon, and/or a 3:00 snack are necessary. Although the tumor may be stimulated occasionally to secrete insulin by the ingestion of carbohydrates, it is inadvisable to restrict the intake of carbohydrate. More slowly absorbable forms of carbohydrates (e.g. starches, bread, potatoes, rice) generally are preferred. During hypoglycemic episodes, rapidly absorbable forms (e.g. fruit juices with added glucose or sucrose) are indicated. In patients with severe refractory hypoglycemia, use of a continuous intravenous infusion of glucose, coupled with increased dietary intake of carbohydrate, frequently alleviates hypoglycemia long enough to institute additional therapy.

DIAZOXIDE AND NATRIURETIC BENZOTHIADIAZINES

Diazoxide (Proglycem) owes its potent hyperglycemic properties to two effects (48) (49): it directly inhibits the release of insulin by β cells through stimulation of α-adrenergic receptors, and it has an extrapancreatic hyperglycemic effect, probably by inhibiting cyclic adenosine monophosphate phosphodiesterase (cyclic AMP), resulting in higher plasma levels of cyclic AMP and enhanced glycogenolysis. Because diazoxide induces the retention of sodium, edema is troublesome at higher dosages. The addition of a diuretic benzothiadiazine (e.g., hydrochlorothiazide) not only corrects or prevents edema but synergizes the hyperglycemic effect of diazoxide. At the doses needed to counteract the higher doses of diazoxide (e.g. 450-

600 mg/d), natriuretic benzothiadiazines frequently induce hypokalemia. Nausea is an additional complication at higher dosages of diazoxide, and hypertrichosis may complicate long-term treatment. These compounds have been useful to elevate blood levels of glucose into the euglycemic range if operation must be delayed for weeks or months. Patients with benign insulinomas have been managed successfully for up to 16 years with diazoxide in doses of 150 to 450 mg/d in combination with hydrochlorothiazide in doses of 25-200mg/d. If they can be tolerated, higher doses may be used in patients with malignant insulinomas.

CALCIUM CHANNEL BLOCKERS

Theoretically, calcium channel blockers are capable of inhibiting insulin secretion. Verapamil has been used successfully to alleviate the hypoglycemia caused by an insulin-secreting pancreatic tumor in a 94-year-old woman (50). Verapamil and diltiazem have been used with variable results in other patients with organic hyperinsulinism.

PROPRANOLOL

β-Adrenergic-receptor blocking drugs inhibit insulin secretion and therefore may be of value in treating organic hyperinsulin. Only a few reports of the use of propranolol have appeared (51) (52). Its use has been associated with the reduction of plasma insulin levels and with the relief of hypoglycemic attacks in patients with benign or malignant insulinoma. In a patient with a benign insulinoma, 80 mg of propranolol a day was sufficient, whereas a patient with malignant insulinoma, in whom streptozotocin was no longer effective, required 640 mg of propranolol orally per day (52). Because this drug can mask the adrenergic symptoms of hypoglycemia and inhibit muscle glycogenolysis, however, there is a risk of aggravating the clinical syndrome. The drug should be used with extreme caution and careful monitoring.

DILANTIN

The anticonvulsive diphenylhydantoin (Dilantin) has been shown to inhibit the in vitro release of insulin from both the labile and storage β-cell pools. It has been used successfully to control refractory hypoglycemia, as evidenced by normal (53) (54). In only one-third or less of patients with benign insulinoma, however, is the hyperglycemic effect of Dilantin of any clinical significance. Furthermore, with the dosage required, ataxia, nystagmus, hypertrophic gums, and megaloblastic anemia may be side effects. Maintenance doses range from 300 to 600 mg/d. The concurrent administration of diazoxide lowers measurable blood levels of dilantin, and their concurrent use is not recommended.

LONG-ACTING SOMATOSTATIN ANALOGUES

We initially reported the successful use of octreotide (Sandostatin) in prolonging the ability to fast in a patient with a benign insulinoma, (55) and a similar experience was reported by Osei and O'Dorisio (56) in a patient with a malignant tumor. Our more recent experience has shown a variety of responses not easily predictable by the clinical or biochemical profile. We have

examined the effects of a long-acting octreotide analogue in seven patients with endogenous hyperinsulinism: five with proven single adenomas, one with multiple adenomas, and one with organic hyperinsulinism associated with MEN-1 (29). In two patients, and possibly a third, octreotide prolonged the ability to fast without hypoglycemia, with variable decreases in plasma insulin concentrations. A trial of long-term administration of octreotide in one of these patients gave only short-term relief of hypoglycemia. Octreotide did not improve, or actually worsened, plasma glucose levels on fasting in the other four patients. In contrast, oral administration of diazoxide to four of these patients was effective in raising plasma glucose levels. A child treated for nesidioblastosis did well initially but subsequently required pancreatectomy and also grew at only the third percentile. It is unlikely that octreotide will be a useful addition to the therapeutic armamentarium for treatment of organic hyperinsulinism, except in familial forms of nesidioblastosis. Others have reported that about 50% of people would respond and this did not require a positive octreoscan since the drug is capable of altering insulin secretion without changing tumor burden (57).

In the Clarinet trial Caplin and collegues reported on 91 patients with PET tumors and the response to Lanreotide showed a reduction of the hazard ratio of 0.48 indicating a 52% improvement over placebo (58).

mTOR INHIBITORS

Targeting the pathway of the mammalian target of rapamycin (mTOR) has been shown in several trials to be effective in the management of neuroendocrine tumors. Several studies have recently shown that everolimus (10mg/day) can normalize blood glucose levels in insulinoma patients with a median progression to hypoglycemia of 6.5 months (59) (60). Moreover as indicated below the use of Rapamycin prolonged the life of a patient for 12 months without hypoglycemia when all other treatment had failed (9).

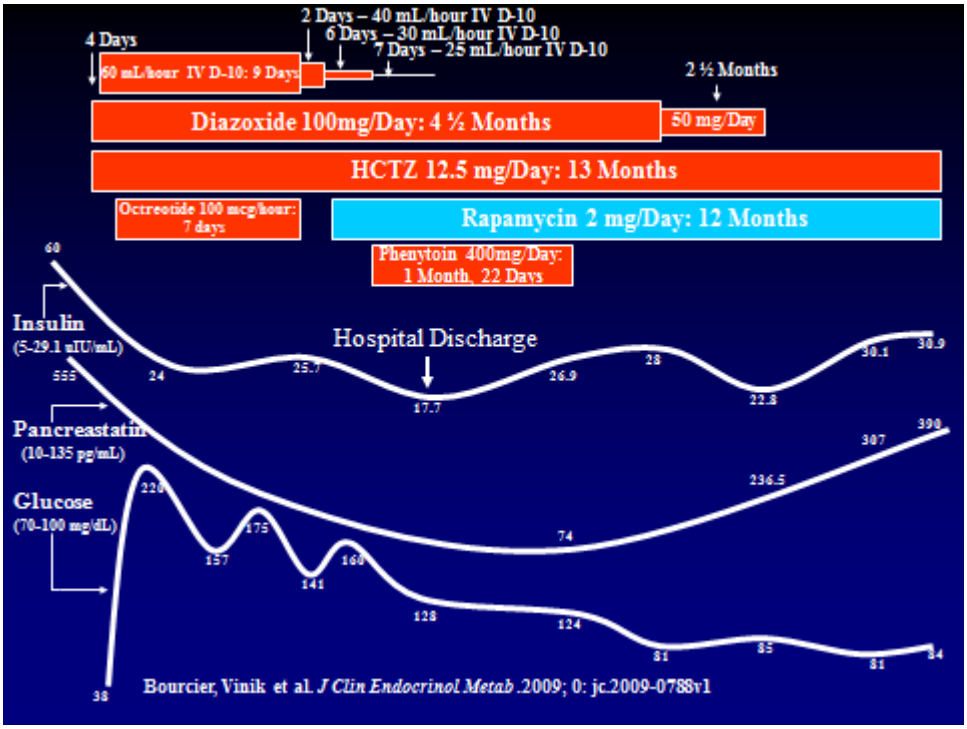
TYROSINE KINASE INHIBITORS

The oral multi-kinase inhibitor sunitinib malate (25mg/day x 4 weeks, off 2 weeks) has been reported in one case report to improve symptoms of hypoglycemia and provide stable disease for 2 years (61). However TKIs do not have the capacity to suppress insulin, as well as inducing insulin resistance, and thus when faced with this choice one favors the use of Rapamycin (9) or everolimus which do have the capacity to prevent hypoglycemia (62).

Figure 1 illustrates the complexity of management of a patient with malignant hyperinsulinism which ultimately required the MTOR inhibitor Rapamycin to control the hypoglycemia. The patient was an 86 y Caucasian male with a pancreatic islet cell tumor presenting 4years before and underwent a distal pancreatectomy and splenectomy. Liver metastases 1 ½ years later – no evidence of tumors at any other metastatic sites. Hypoglycemia was now getting worse with excursions in the 20 mg/dL range. Some of these episodes resulted in the patient losing consciousness. Patient wanted to maintain a good quality of life and still treat his condition. The course of his disease was quite eventful. Biomarker levels started increasing – Pancreatic

Polypeptide – 2,659 pg/mL; Calcitonin – 15.5 pg/mL; IGF-1 – 74 ng/mL; Neurokinin A – 93 pg/mL and Pancreastatin – 555 pg/mL The patient's fasting blood glucose levels declined to the 20-40 mg/dL range despite starting diazoxide 100 mg/day, HCTZ 12.5 mg/day and increasing the frequency of meals to every 1-2 hours. He was admitted after losing consciousness with a blood sugar level of 19 mg/dL. Hypoglycemia stabilized with 10% dextrose (D-10) infused at 60 ml/hour in the hospital. The figure illustrates the ineffective ness of somatostatin and all other therapies but significant improvement with Rapamycin which reduce the insulin levels from 60 to 30uU/ml, increased insulin resistance HOMA-IR from 4.8 to 6.4 and blood glucose levels rose from 38 to 84 mg/dl.

Figure 1. Complexities of the Management of Hypoglycemia in a patient with Malignant Insulinoma (9)



This 86-year old gentleman with a malignant insulinoma and intractable hypoglycemia initially required diazoxide 100 mg/day, Rapamycin 2 mg/day, hydrochlorothiazide 12.5 mg/day, phenytoin 400 mg/day and a constant infusion of glucose (D-10 at 60 cc/hour) to control the hypoglycemia and elevated insulin levels. He became intolerant to all hyperglycemic agents except for the thiazide diuretic and Rapamycin and has maintained euglycemia for greater than 1 year with a reduction of circulating insulin levels and no evidence of tumor progression based on Octreoscan®. Rapamycin therapy increased his insulin resistance along with a 50% reduction in circulating insulin levels. Biochemically, the pancreastatin and insulin levels have risen, suggesting some tumor growth/secretion

GLUCOCORTICOIDS

The use of glucocorticoids, which increase gluconeogenesis and cause insulin resistance, also can help to stabilize blood glucose at an acceptable level. Pharmacologic doses (prednisone, approximately 1 mg/kg) must be used.

GLUCAGON

Glucagon may help to raise blood glucose concentrations, but it may simultaneously directly stimulate the release of insulin.

ESTROGEN RECEPTOR BLOCKERS

Recent data suggest that estrogen and progesterone receptors are frequently expressed in insulinomas and that these receptors appear to be functional (63). However, whether or not estrogen receptor blockers can effectively decrease insulin levels in these patients is not known. The American Joint Committee on Cancer has developed a new staging system for pancreatic neoplasms and the 5 and 10y survival rates for people who have undergone resection of a pancreatic neuroendocrine tumor is given in Table 7 (64) (65). Management of the less common malignant hyperinsulinism is dealt with in detail in the Chapter on management of malignant pancreatic neuroendocrine tumors. Of note CT-guided radiofrequency ablation has been reported to manage elderly patients in poor physical condition (66). Everolimus has been shown to reduce hypoglycemic episodes in 4 patients (67) and a French group normalized blood glucose levels in 11/12 patients with malignant metastatic tumors for a mean of 6.5 months (range 1-35 months). However three patients discontinued treatment because of cardiac and or pulmonary adverse events that led to 2 deaths (59). For more detail on surgical and radiotherapeutic approaches see Vinik et al (68).

Table 7. Five- and ten-year survival rates for patients who underwent resection of a pancreatic neuroendocrine tumor (69)

Stages	Prognostic stages	Observed survival*		Relative survival¶		Median survival (months)
		5-year %	10-year %	5-year %	10-year %	
I	T1 no MO	61.0	46.0	75.6	71.1	112
II	T2 no MO	52.0	28.8	64.3	45.8	63
	or T3					
III	T4 no MO	41.4	18.5	60.5	33.1	46
IV	Any T M1	15.5	5.1	19.9	8.9	14

*Comparisons between each stage group are significant to $p<0.0001$. From Bilimoria et al (61)
¶Survival adjusted for patient age by matching against 1990 United States Census Bureau data.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc. See Table 8 for staging.

Table 8. TNM staging system for exocrine and endocrine tumors of the pancreas

Primary Tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ*		
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension		
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph nodes metastasis		
N1	Regional lymph nodes metastasis		
Distant metastases (M)			
M0	No distant metastasis		
M1	Distant metastasis		
Anatomic stage/prognostic groups			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N1	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

Note: cTNM is the clinical classification, pTNM is the pathologic classification.

* This includes lesions classified as PanIn III classification.

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REFERENCES

1. Fajans SS, Vinik AI. Diagnosis and treatment of insulinoma. In: Fanten RJ, Manni A, editors. Diagnosis and Management of Endocrine Related Tumors. Boston: Martinus Nijhoff, 1984: 235.
2. Redmon JB, Nuttall FQ. Autoimmune hypoglycemia. Endocrinol Metab Clin North Am 1999; 28(3):603-18, vii.
3. Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI, Gorden P. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. Medicine (Baltimore) 2002; 81(2):87-100.
4. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P. Autoimmune forms of hypoglycemia. Medicine (Baltimore) 2009; 88(3):141-153.
5. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV. Hyperinsulinemic hypoglycemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 2005; 353(3):249-254.
6. Anlauf M, Wieben D, Perren A et al. Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol 2005; 29(4):524-533.
7. Service JF, Vella A. Insulinoma. Up To Date 2017;1-13.
8. Won JG, Tseng HS, Yang AH et al. Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS). Clin Endocrinol (Oxf) 2006; 65(5):566-578.
9. Bourcier ME, Sherrod A, DiGuardo M, Vinik AI. Successful control of intractable hypoglycemia using rapamycin in an 86-year-old man with a pancreatic insulin-secreting islet cell tumor and metastases. J Clin Endocrinol Metab 2009; 94(9):3157-3162.
10. Cryer PE. Hypoglycemia, functional brain failure, and brain death. J Clin Invest 2007; 117(4):868-870.
11. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care 2003; 26(6):1902-1912.
12. Meneilly GS, Cheung E, Tuokko H. Altered responses to hypoglycemia of healthy elderly people. J Clin Endocrinol Metab 1994; 78(6):1341-1348.
13. Edis AJ, McIlrath DC, van Heerden JA et al. Insulinoma--current diagnosis and surgical management. Curr Probl Surg 1976; 13(10):1-45.
14. Friesen SR. Treatment of the Zollinger-Ellison syndrome. A 25 year assessment. Am J Surg 1982; 143(3):331-338.
15. Thompson NW, Eckhauser FE. Malignant islet-cell tumors of the pancreas. World J Surg 1984; 8(6):940-951.
16. Thompson NW. The surgical treatment of islet cell tumors of the pancreas. Pancreatic Disease. Grune & Stratton, 1981.
17. Glaser B, Shapiro B, Glowniak J, Fajans SS, Vinik AI. Effects of secretin on the normal and pathological beta-cell. J Clin Endocrinol Metab 1988; 66:1138-1143.
18. Portela-Gomes GM, Stridsberg M, Grimelius L, Rorstad O, Janson ET. Differential expression of the five somatostatin receptor subtypes in human benign and malignant insulinomas - predominance of receptor subtype 4. Endocr Pathol 2007; 18(2):79-85.

19. Vinik A. Endocrine tumors of the gastroenteropancreatic axis. Diagnosis and Management of Endocrine-Related Tumors. 1984.
20. Vinik A, Strodel W, Cho K, Eckhauser F, Thompson N. Localization of hormonally active gastrointestinal tumors. Endocrine Surgery Update 1983.
21. Glowniak JV, Shapiro B, Vinik AI, Glaser B, Thompson NW, Cho KJ. Percutaneous transhepatic venous sampling of gastrin: value in sporadic and familial islet-cell tumors and G-cell hyperfunction. N Engl J Med 1982; 307:293-297.
22. Kaplan EL, Lee CH. Recent advances in the diagnosis and treatment of insulinomas. Surg Clin North Am 1979; 59(1):119-129.
23. Le Quesne LP, Nabarro JD, Kurtz A, Zweig S. The management of insulin tumours of the pancreas. Br J Surg 1979; 66(6):373-378.
24. Modlin IM. Endocrine tumors of the pancreas. Surg Gynecol Obstet 1979; 149(5):751-769.
25. Gouya H, Vignaux O, Augui J et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. AJR Am J Roentgenol 2003; 181(4):987-992.
26. Goh BK, Ooi LL, Cheow PC et al. Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. J Gastrointest Surg 2009; 13(6):1071-1077.
27. Sotoudehmanesh R, Hedayat A, Shirazian N et al. Endoscopic ultrasonography (EUS) in the localization of insulinoma. Endocrine 2007; 31(3):238-241.
28. Joseph AJ, Kapoor N, Simon EG et al. Endoscopic ultrasonography--a sensitive tool in the preoperative localization of insulinoma. Endocr Pract 2013; 19(4):602-608.
29. Stefanini P, Carboni M, Patrassi N, Basoli A. Beta-islet cell tumors of the pancreas: results of a study on 1,067 cases. Surgery 1974; 75(4):597-609.
30. Robins JM, Bookstein JJ, Oberman HA, Fajans SS. Selective angiography in localizing islet-cell tumors of the pancreas. A further appraisal. Radiology 1973; 106(3):525-528.
31. Gibril F, Reynolds JC, Doppman JL et al. Somatostatin receptor scintigraphy: its sensitivity compared with that of other imaging methods in detecting primary and metastatic gastrinomas. A prospective study. Ann Intern Med 1996; 125(1):26-34.
32. Doppman JL, Miller DL, Chang R, Shawker TH, Gorden P, Norton JA. Insulinomas: localization with selective intraarterial injection of calcium. Radiology 1991; 178(1):237-241.
33. Cho KJ, Vinik AI, Thompson NW et al. Localization of the source of hyperinsulinism: percutaneous transhepatic portal and pancreatic vein catheterization with hormone assay. Am J Roentgenol 1982; 139:237-245.
34. Ingemansson S, Kuhl C, Larsson LI, Lunderquist A, Lundquist I. Localization of insulinomas and islet cell hyperplasias by pancreatic vein catheterization and insulin assay. Surg Gynecol Obstet 1978; 146(5):724-734.
35. Katz LB, Aufses AH, Jr., Rayfield E, Mitty H. Preoperative localization and intraoperative glucose monitoring in the management of patients with pancreatic insulinoma. Surg Gynecol Obstet 1986; 163(6):509-512.
36. Vinik AI, Thompson N. Controversies in the management of Zollinger-Ellison syndrome. Ann Intern Med 1986; 105:956-959.
37. Wild D, Macke H, Christ E, Gloor B, Reubi JC. Glucagon-like peptide 1-receptor scans to localize occult insulinomas. N Engl J Med 2008; 359(7):766-768.

38. Christ E, Wild D, Ederer S et al. Glucagon-like peptide-1 receptor imaging for the localisation of insulinomas: a prospective multicentre imaging study. Lancet Diabetes Endocrinol 2013; 1(2):115-122.
39. McAuley G, Delaney H, Colville J et al. Multimodality preoperative imaging of pancreatic insulinomas. Clin Radiol 2005; 60(10):1039-1050.
40. Hardy OT, Hernandez-Pampaloni M, Saffer JR et al. Accuracy of [18F]fluorodopa positron emission tomography for diagnosing and localizing focal congenital hyperinsulinism. J Clin Endocrinol Metab 2007; 92(12):4706-4711.
41. Kauhanen S, Seppanen M, Minn H et al. Fluorine-18-L-dihydroxyphenylalanine (18F-DOPA) positron emission tomography as a tool to localize an insulinoma or beta-cell hyperplasia in adult patients. J Clin Endocrinol Metab 2007; 92(4):1237-1244.
42. Ravi K, Britton BJ. Surgical approach to insulinomas: are pre-operative localisation tests necessary? Ann R Coll Surg Engl 2007; 89(3):212-217.
43. Nikfarjam M, Warshaw AL, Axelrod L et al. Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 2008; 247(1):165-172.
44. Pasieka JL, McLeod MK, Thompson NW, Burney RE. Surgical approach to insulinomas. Assessing the need for preoperative localization. Arch Surg 1992; 127(4):442-447.
45. Tseng LM, Chen JY, Won JG et al. The role of intra-arterial calcium stimulation test with hepatic venous sampling (IACS) in the management of occult insulinomas. Ann Surg Oncol 2007; 14(7):2121-2127.
46. Grover AC, Skarulis M, Alexander HR et al. A prospective evaluation of laparoscopic exploration with intraoperative ultrasound as a technique for localizing sporadic insulinomas. Surgery 2005; 138(6):1003-1008.
47. Sweet MP, Izumisato Y, Way LW, Clark OH, Masharani U, Duh QY. Laparoscopic enucleation of insulinomas. Arch Surg 2007; 142(12):1202-1204.
48. Fajans SS, Floyd JC, Jr., Knopf RF, Rull J, Guntsche EM, Conn JW. Benzothiadiazine suppression of insulin release from normal and abnormal islet tissue in man. J Clin Invest 1966; 45(4):481-492.
49. Fajans SS, Floyd JC, Jr., Thiffault CA, Knopf RF, Harrison TS, Conn JW. Further studies on diazoxide suppression of insulin release from abnormal and normal islet tissue in man. Ann N Y Acad Sci 1968; 150(2):261-280.
50. Ulbrecht JS, Schmeltz R, Aarons JH, Greene DA. Insulinoma in a 94-year-old woman: long-term therapy with verapamil. Diabetes Care 1986; 9(2):186-188.
51. Blum I, Doron M, Laron Z, Atsmon A, Tiqva P. Prevention of hypoglycemic attacks by propranolol in a patient suffering from insulinoma. Diabetes 1975; 24(6):535-537.
52. Schusdziarra V, Zyznar E, Rouiller D et al. Splanchnic somatostatin: a hormonal regulator of nutrient homeostasis. Science 1980; 207(4430):530-532.
53. Brodows RG, Campbell RG. Control of refractory fasting hypoglycemia in a patient with suspected insulinoma with diphenylhydantoin. J Clin Endocrinol Metab 1974; 38(1):159-162.
54. Hofeldt FD, Dippe SE, Levin SR, Karam JH, Blum MR, Forsham PH. Effects of diphenylhydantoin upon glucose-induced insulin secretion in three patients with insulinoma. Diabetes 1974; 23(3):192-198.

55. Tsai ST, Eckhauser FE, Thompson NW, Strodel WE, Vinik AI. Perioperative use of long-acting somatostatin analog (SMS 201-995) in patients with endocrine tumors of the gastroenteropancreatic axis. Surgery 1986; 100:788-795.
56. Osei K, O'Dorisio TM. Malignant insulinoma: effects of a somatostatin analog (compound 201-995) on serum glucose, growth, and gastro-entero-pancreatic hormones. Ann Intern Med 1985; 103(2):223-225.
57. Arnold CN, Sosnowski A, Schmitt-Graff A, Arnold R, Blum HE. Analysis of molecular pathways in sporadic neuroendocrine tumors of the gastro-entero-pancreatic system. Int J Cancer 2007; 120(10):2157-2164.
58. Caplin ME, Pavel M, Cwikla JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014; 371(3):224-233.
59. Bernard V, Lombard-Bohas C, Taquet MC et al. Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycemia. Eur J Endocrinol 2013; 168(5):665-674.
60. Fiebrich HB, Siemerink EJ, Brouwers AH et al. Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. Oncologist 2011; 16(6):783-787.
61. Chen J, Wang C, Han J et al. Therapeutic effect of sunitinib malate and its influence on blood glucose concentrations in a patient with metastatic insulinoma. Expert Rev Anticancer Ther 2013; 13(6):737-743.
62. Kulke MH, Bergsland EK, Yao JC. Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med 2009; 360(2):195-197.
63. Alabraba EB, Taniere P, Reynolds GM, Stewart PM, Wigmore SJ, Bramhall SR. Expression and functional consequences of oestrogen and progesterone receptors in human insulinomas. Endocr Relat Cancer 2007; 14(4):1081-1088.
64. Bilimoria KY, Bentrem DJ, Ko CY et al. Validation of the 6th edition AJCC Pancreatic Cancer Staging System: report from the National Cancer Database. Cancer 2007; 110(4):738-744.
65. Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis. Ann Surg Oncol 2017; 24(7):2023-2030.
66. Limmer S, Huppert PE, Juette V, Lenhart A, Welte M, Wietholtz H. Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycemia. Eur J Gastroenterol Hepatol 2009; 21(9):1097-1101.
67. Yao JC, Fazio N, Singh S et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016; 387(10022):968-977.
68. Vinik AI. Advances in diagnosis and treatment of pancreatic neuroendocrine tumors. Endocr Pract 2014; 20(11):1222-1230.
69. Bilimoria KY, Bentrem DJ, Merkow RP et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. J Am Coll Surg 2007; 205(4):558-563.