**INSULINOMA**

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**Updated October 24, 2020**

**ABSTRACT**

Insulinomas are rare pancreatic neuroendocrine neoplasms (panNENs - incidence of 1-3 cases per million per year). Most are solitary and do not show signs of malignant spread. Multiple synchronous or metachronous panNENs / insulinomas may occur in multiple endocrine neoplasia type 1 (MEN-1). The diagnosis of an insulinoma requires demonstration of inappropriately high insulin, proinsulin, or C-peptide levels for the prevailing hypoglycemia in a 72h fast. Localization of the tumor and exclusion or confirmation of metastatic disease by computed tomography is the preferred initial option followed by endoscopic ultrasonography (EUS) or MRI. Glucagon-like peptide receptor 1 (GLP-1R) receptor positron emission tomography (PET) CT is a most promising new localization technique, but regretfully not widely available yet. For single solitary tumors surgical excision is the treatment of choice. In malignant cases, debulking of the panNENs, including locoregional lymph nodes can be considered. If hyperinsulinemia and hypoglycemia persist, diazoxide with a thiazide diuretic relieves hypoglycemia. Liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability. In patients with unresectable low-grade metastatic malignant insulinomas, the long-acting somatostatin analog Lanreotide Autogel is the approved first-line therapy for control of tumor growth and sometimes control of hypoglycemia is achieved with this drug. If indicated, peptide receptor radiotherapy (PRRT) with radiolabeled somatostatin analogs, or Everolimus can be used for tumor, symptom and biochemical control. Malignant NENs can also be treated with cytotoxic chemotherapy regimens, particularly those with a high tumor grade.

**HISTORY**

The pancreatic islet cells were first described by the German medical student Paul Langerhans (1847-1888) in 1869. James R Macleod (1876-1935), Frederick G. Banting (1891-1941), Charles H. Best (1899-1978), and James B. Collip (1892-1965) first isolated insulin in 1922. The US surgeon Seale Harris (1870-1957) was the first to identify a case of endogenous hyperinsulinism. In 1926, the US surgeon William J Mayo (1861-1939) performed an exploratory laparotomy on a patient with recurrent severe hypoglycemia and found an unresectable pancreatic tumor (malignant insulinoma) with multiple liver, lymph node and mesenteric metastases. In 1927, the US physician Russel M. Wilder (1885-1959) and colleagues reported on the necropsy of this patient. Extracts of a liver metastasis produced marked lowering of the blood glucose levels when injected into rabbits. It seems also likely that Mayo’s & Wilder’s patient had multiple endocrine neoplasia type 1 (MEN-1) since he also had renal stones and his cousin had had similar symptoms. In 1954, the US internist Paul Wermer (1898-1975) reported disorders of one or more endocrine glands in five members of one family in 1954. This familial syndrome was once called Wermer syndrome, but is nowadays better known as multiple endocrine neoplasia type 1 (MEN-1).

The first cure of hyperinsulinism by removal of an insulinoma by the Canadian surgeon Roscoe R. Graham (1890-1948) was reported in 1929 by Goldwin Howland (1875-1950) and co-workers. The US surgeon Allen O. Whipple (1881-1963) and pathologist Virginia K. Frantz (1896-1967) identified the diagnostic hallmark of insulinoma better known as “Whipple’s triad” (1).

**INTRODUCTION**

Insulinomas are the most common hormone-producing neuroendocrine neoplasms (NENs) of the pancreas, with an estimated incidence of 1–3 per million per year. There is an age-specific incidence peak in the fifth decade of life and the incidence is slightly higher in women than in men. Approximately 10% are multiple, less than 10% show malignant spread, and 5–10% are associated with the MEN-1 syndrome. MEN-1 related NENs / insulinomas may occur as multiple lesions. Fifty percent of MEN-1 patients harbor pancreatic NENs (panNENs) (2-6).

After initial recognition of the key symptoms, careful laboratory testing, sophisticated imaging and eventually meticulous surgery follows in most cases. It is evident that a multidisciplinary team (MDT) approach is required. The hallmark features of insulinomas resulting from hypoglycemia include neuroglycopenic (e.g. confusion, visual changes, unusual behavior) and sympatheticoadrenal (e.g. palpitations, diaphoresis, tremulousness) symptoms. Usually there is a gradual increase in weight because of increased intake of carbohydrates, but this is not obligatory. 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 (2-5) (see chapter in the Diabetes section entitled “Non-Diabetic Hypoglycemia” (15).

**CLINICAL FEATURES**

The hallmark of the diagnosis of insulinoma is Whipple’s triad: 1) symptoms known or likely to be caused by hypoglycemia, 2) a low plasma glucose measured at the time of the symptoms and 3) relief of symptoms when the glucose is raised back to normal. The principal biochemical feature of an insulinoma is hypoglycemia but there are other malignancies and disorders which can cause hypoglycemia like big-IGF-2-producing tumors, glycogen storage diseases, administration of exogenous insulin or sulfonylureas, insulinomatosis and nesidioblastosis in the pancreas. While hypoglycemia is a hallmark of insulinoma, the low 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 1) (4, 7-18).

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| **Table 1. Distinguishing Sign and Symptoms of Insulinomas** | |
| **Neurogenic** | **Neuroglycopenic** |
| · **Adrenergic**  Palpitations  Tremor  Anxiety/arousal/nervousness  · **Cholinergic**  Sweating/diaphoresis  Hunger  Paresthesia  Circumpolar tingling | · Blurred Vision  · Cognitive impairments  · Behavioral changes  · Psychomotor abnormalities  · Confusion  · Disorientation  · Memory Loss  · Seizure  · Stupor |

**BIOCHEMICAL DIAGNOSIS**

The first step in the diagnosis of an insulinoma is to demonstrate hyperinsulinemic hypoglycemia (this is also called “organic hyperinsulinism”). This can potentially be achieved during a spontaneous hypoglycemia. However, most frequently a 72-hour fast is needed, which is currently the standard test to diagnose an insulinoma. The patient is closely clinically observed while serial glucose and insulin levels are obtained over the 72 hours until the patient becomes symptomatic or hypoglycemia is demonstrated. More than 95% of cases can be diagnosed based on responses to this easy test. Because the absolute insulin level is not elevated in all patients with insulinomas, a nondetectable or nonelevated insulin level does not rule out the disease. Values of insulin equal to or greater than 3 μU/mL (using modern insulin assays) in the presence of a blood glucose less than 3 mmol/l (55 mg/dl) are highly suggestive. Most specialists prefer more stringent cut-off glucose values amounting to 2.2 mmol/L (40 mg/dL) or less to increase the diagnostic specificity. Because of the potential of increased proinsulin secretion, which is not detected using the currently used insulin assays, it is generally recommended also to measure proinsulin and/or C-peptide levels, particularly in those cases with low to undetectable insulin levels in the blood. In the past these elevated proinsulin levels were also detected using the insulin RIAs, whereas nowadays these tumors are inadvertently addressed as pro-insulinomas. In these cases, concomitant C-peptide levels equal to or greater than 0.2 nmol/l and/or concomitant pro-insulin levels equal to or greater than 5 pmol/l (in the presence of a hypoglycemia) are also suggestive of an insulinoma. Commercial insulin preparations do not contain C-peptide and low C-peptide levels combined with high insulin levels confirm the diagnosis of factitious hyperinsulinemia.

Most drugs used to treat type 2 diabetes do not cause severe hypoglycemia. Insulin, sulfonylureas, and meglitinides can cause severe hypoglycemia while metformin, thiazolidinediones, alpha glucosidase inhibitors, inhibitors of dipeptidyl peptidase 4 (DPP-4 inhibitors or gliptins), SGLT2 inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists or incretin mimetics) typically do not cause severe hypoglycemia when used as monotherapy (see chapter in the Diabetes section entitled “Non-Diabetic Hypoglycemia” (15).

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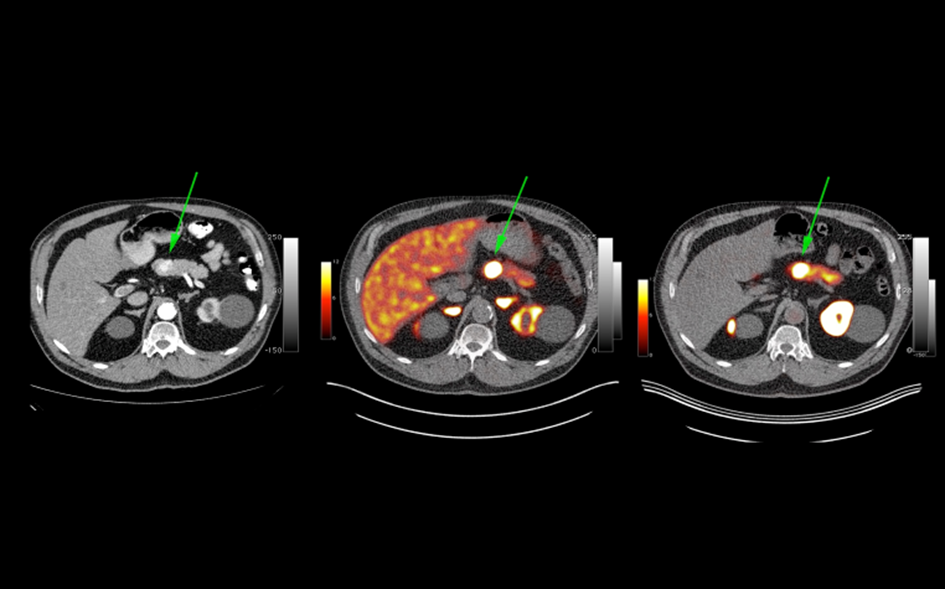
Finally, the demonstration of ß-hydroxy-butyrate levels equal to or less than 2.7 mmol/l at the end of the fast is used by some to confirm the hyperinsulinemic state. Some experts require the demonstration of a glucose response to 1 mg. glucagon of more than 1.4 mmol/l (25 mg/dl) at the end of the fast. This increase of glucose is illustrative for the hyperinsulinemic state, because hyperinsulinemia preserves the liver glycogen storage despite fasting (4, 7-18).

**TUMOR LOCALIZATION**

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, the latter particularly is present in MEN-1 patients. In addition, 10 to 15% are malignant and very few patients will have either islet cell hyperplasia, or nesidioblastosis and no visible tumor at all. The anatomical localization of nonmetastatic (benign) insulinomas is also important for the choice between laparoscopic, robot-assisted and open pancreatic surgery and between enucleation or resection – partial pancreatectomy. Techniques most commonly used to demonstrate tumors in the pancreas include 3 phase CT and MRI, and endoscopic ultrasound (EUS). Each modality has variable reported abilities to identify insulinomas, likely reflecting institutional or operator-dependent (like in EUS) expertise (Table 2).

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| **Table 2. Imaging Strategies in Insulinoma Patients** | |
|  | **Sensitivity** |
| Three phase CT  MRI (T1 +T2 weighted images + fat suppression)  Endoscopic Ultrasound (EUS)  Arterial Calcium Stimulation - Venous Sampling | 60-80%  85-90%  75-90%  80-90% |
| **Intraoperative localizing techniques**  Palpation  Intraoperative ultrasound (IOUS)  Palpation plus IOUS | 70%  75-90%  85-95% |
| **Nuclear medicine**  Somatostatin receptor imaging SPECT / PET  18F-DOPA PET  Glucagon-Like Peptide-1 (Exendin-4) receptor Imaging SPECT / PET | 46-50%/50-86%  50%  75/95% |

Until recently, selective pancreatic angiography and elective intra-arterial injection of calcium with sampling of hepatic vein insulin were used on a regular basis in high volume centers. These invasive regionalization (an exact localization will be never given) procedures became less used because of the improved imaging procedures mentioned above and the recent introduction of glucagon-like peptide 1 (GLP-1) receptor imaging. The glucagon-like peptide 1 receptor (GLP-1R) is mainly expressed on the pancreatic beta cells and is therefore an interesting target for imaging of (previously occult) insulinomas. However, as opposed to benign insulinomas, malignant insulinomas often lack the GLP-1R. Conversely, malignant insulinomas often do express the somatostatin receptor subtype 2 (SST2), which can be targeted using PET/CT or PET/MRI using 68Ga-DOTA-labeled somatostatin analogs (SSAs) or with somatostatin receptor scintigraphy and SPECT. In various studies, the GLP-1 receptor agonists 111In-DOTA-exendin-4 and/or 68Ga-DOTA-exendin-4 PET/CT successfully detected benign insulinomas. 68Ga-DOTA-exendin-4 PET/CT seems more sensitive than 111In-DOTA-exendin-4 SPECT/CT. Replacing DOTA by NODAGA for 68Ga-NODAGA-exendin-4 PET/CT ensures higher specific activities (Figure 1).



# **Figure 1. From left to right: arterial-phase contrast-enhanced CT, 68Ga-DOTATATE PET-CT, 68Ga-NODAGA-exendin PET-CT (Courtesy: Drs. Marti Boss and Martin Gotthardt, Radboud University Medical Centre, Nijmegen, the Netherlands).**

The efficacy of fluorine-18-L-3,4-dihydroxyphenylalanine (18F-DOPA) PET/CT is based on co-secretion of dopamine and hormones or peptides by NEN cells. In these cells, L-DOPA is converted by the enzyme L-DOPA decarboxylase to dopamine. 18F-DOPA PET/CT (with carbidopa premedication) plays an important role in the differential diagnosis of congenital hyperinsulinism (nesidioblastosis), especially for the identification of focal forms.

If all localization and regionalization techniques fail to localize a tumor, intraoperative palpation of the pancreas and ultrasound might prove to be successful (19 -27).

In addition to the assessment of insulin hypersecretion, the metastatic spread, as reflected by the (ENETS/AJCC-UICC) staging, also determines the clinical manifestations and contributes to the prognosis (Tables 3 and 4) (28-31). Secondary, or metachronous insulin secretion by pancreatic neuroendocrine tumors which previously were non-secreting, or secreted other peptide hormones can also occur and is generally associated with poor survival (32-33).

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| **Table 3. TNM Staging System for Pancreatic Neuroendocrine Tumors Including Insulinomas** | | |
|  | **ENETS** | **AJCC -UICC** |
|  | **T Primary Tumor** | **T Primary Tumor** |
| TX | Primary tumor cannot be assessed | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor | No evidence of primary tumor |
| T1 | Tumor limited to the pancreas and size <2 cm | Tumor limited to the pancreas, ≤2 cm in greatest dimension |
| T2 | Tumor limited to the pancreas and size 2 - 4 cm | Tumor limited to the pancreas, >2 cm in greatest dimension |
| T3 | Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct | Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery |
| T4 | Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of celiac axis or superior mesenteric artery | Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor) |
|  | **(N) Regional Lymph Nodes** | **(N) Regional Lymph Nodes** |
| NX | Regional lymph nodes cannot be assessed | Regional lymph nodes cannot be assessed |
| NO | No regional lymph node metastasis | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis | Regional lymph node metastasis |
|  | **(M) Distant Metastases** | **(M) Distant Metastases** |
| MX | Distant metastasis cannot be assessed |  |
| MO | No distant metastasis | No distant metastasis |
| M1 | Distant metastasis | Distant metastasis |

ENETS= European Neuroendocrine Tumor Society; AJCC -UICC= American Joint Committee on Cancer/Union for International Cancer Control

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| **Table 4. Anatomic Stage/Prognostic Groups** | | | |
| **Stage** | **T** | **N** | **M** |
| I | T1 | N0 | M0 |
| IIa | T2 | N0 | M0 |
| IIb | T3 | N0 | M0 |
| IIIa | T4 | N0 | M0 |
| IIIb | Any T | N1 | M0 |
| IV | Any T | Any N | M1 |

**HISTOPATHOLOGY**

The 2017 WHO classification and grading of panNENs now separates these tumors using the Ki67 index (MIB-1 antibody staining) into 2 broad categories: grade 1-2 (G1-2) well-differentiated pancreatic NETs (panNETs) and poorly differentiated pancreatic neuroendocrine carcinomas (NECs – panNECs), while adding a new subcategory of well-differentiated grade 3 (G3) NET to the well-differentiated NET category (Table 5). Helpful for the distinction of NECs from G3 NETs is their overexpression of p53 and loss of expression of Rb1. Insulin staining is not obligatory positive in insulinomas and is usually not necessarily required once the clinical diagnosis is made (28-31).

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| **Table 5. WHO 2017 Classification for Neuroendocrine Neoplasms (NENs) of the Pancreas** | | | |
| **Differentiation** | **Name/ Grade** | **Ki 67 (% of ≥500 cells)** | **Mitotic count (2 mm2)** |
| Well differentiated | NET G1  G2  G3 | <3  3-20  >20 | <2  2-20  >20 |
| Poorly differentiated | NEC (G3)  Small cell type  Large cell type | >20 | >20 |

NET= neuroendocrine tumors; NEC= neuroendocrine carcinomas

**SURGICAL AND INTERVENTIONAL TREATMENT**

The treatment of pancreatic islet β-cell disease usually is surgical; in the great majority of cases, it will provide 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 an 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’s procedure). Precise localization obviates blind pancreatic resection. EUS with special focus on the relationship between the tumor and the pancreatic duct is an excellent tool to guide the surgical decision. Laparoscopic, or robot-assisted enucleation of insulinoma has been shown to be feasible, particularly if the lesion is visualized pre-operatively on CT scan or EUS. In patients who have been unresponsive to medical therapy and in whom 18F-DOPA PET/CT, PTHVS, or intra-arterial calcium stimulation with venous sampling suggests diffuse or multiple sources, such as adenomatosis, nesidioblastosis, or hyperplasia, a resection of at least 80% of the distal pancreas can be indicated. In selected cases curative endoscopic ultrasound-guide radiofrequency ablation (EUS-RFA) of a localized insulinoma can be feasible.

Malignant insulinomas can occasionally be surgically cured when there is localized or oligometastatic disease. Also, liver metastases can be resected or treated by bland or chemo-embolization (TACE), radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE). depending on availability at the institution. If more than 90% of tumor load can be resected, palliative surgery can also be considered. However, most malignant metastatic insulinomas cannot be cured by surgery and require medical antihormonal and antitumor treatment (2-5, 35-38).

**MEDICAL MANAGEMENT**

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 benzothiadiazide. 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. The management of malignant insulinoma is antihormonal and antitumor therapy.

**DIETARY MANAGEMENT**

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 meals. For some, the inclusion of a bedtime (11:00 pm) feeding is sufficient; for others, a midmorning, midafternoon, and/or a 3:00 am snack is necessary. 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 nasogastric tube feeding or intravenous infusion of glucose, coupled with increased dietary intake of carbohydrate, frequently alleviates hypoglycemia long enough to institute additional therapy (4,5,7,8).

**MEDICAL THERAPY**

Diazoxide (Proglycem) owes its potent hyperglycemic properties to two effects: it directly inhibits the release of insulin by β cells through stimulation of α-adrenergic receptors. It also has an extra-pancreatic 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. If they can be tolerated, higher doses may be used in patients with malignant insulinomas.

Theoretically, calcium channel blockers are capable of inhibiting insulin secretion. Verapamil and diltiazem have been used with variable results in patients with organic hyperinsulinism.

β-Adrenergic-receptor blocking drugs inhibit insulin secretion and therefore may be of value in treating organic hyperinsulinism. The use of propranolol has been associated with the reduction of plasma insulin levels and with the relief of hypoglycemic attacks in patients with benign or malignant insulinoma. Because this drug can also 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.

The anticonvulsive diphenylhydantoin has been shown to inhibit the in vitro release of insulin from both the labile and storage β-cell pools. In only one-third or less of patients with benign insulinoma, however, is the hyperglycemic effect of diphenylhydantoin of any clinical significance. Furthermore, adverse effects usually occur with the dosages required. Maintenance doses range from 300 to 600 mg/d. The concurrent administration of diazoxide lowers measurable blood levels of diphenylhydantoin, and their concurrent use is not recommended.

Several reports exist on the successful use of intermediate acting subcutaneous octreotide injections (100-500 µg t.i.d.) in prolonging the ability to fast in a patient with benign and malignant insulinomas. However, long-term administration of depot octreotide (Sandostatin LAR 30 mg / 4wks IM) or lanreotide (Somatuline Autogel 120 mg / 4 weeks deep SC) may give only short-term relief of hypoglycemia. SSAs (somatostatin analogs) may also actually worsen plasma glucose levels probably by inhibiting the counterregulatory glucagon response. SSA treatment in insulinoma and nesidioblastosis patients should, therefore, always be preceded by a clinical trial with intermediate acting subcutaneous octreotide. In a limited number of cases, the second-generation pan-SSA Pasireotide has been successfully used to control hypoglycemia in patients with malignant insulinomas.

Targeting the pathway of the mammalian target of rapamycin (mTOR) has been shown in several trials to be effective in the management of low grade metastatic inoperable neuroendocrine tumors. Several studies have recently shown that Everolimus (10mg/day) can normalize blood glucose levels in insulinoma patients. mTOR inhibitors like Everolimus can reduce insulin secretion and increase insulin resistance. The multi-kinase inhibitor Sunitinib (25mg/day) has only been occasionally reported to improve symptoms of hypoglycemia. TKIs (tyrosine kinase inhibitors) do not have the capacity to suppress insulin, as well as inducing insulin resistance, like Everolimus.

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 may help to raise blood glucose concentrations, but it may simultaneously directly stimulate the release of insulin (4,5,7,8, 39-49).

**ANTI-TUMOR TREATMENT IN MALIGNANT INSULINOMAS**

Like in the other panNEN subtypes, anti-tumor treatments can consist of peptide receptor radiotherapy (PRRT) with radiolabeled beta radiation emitting SSAs, several chemotherapy schedules (For a review see ref 54), and targeted treatment with Everolimus and Sunitinib. PRRT with radiolabeled beta radiation emitting SSAs and, as mentioned above, mTOR inhibitors like Everolimus, are frequently able to successfully control the hypoglycemia in patients with inoperable metastatic insulinomas (45-48, 50-55).

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