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# Insulinomas: Comprehensive Review of Epidemiology, Pathophysiology, Clinical Manifestations, Diagnostic Approaches, and Treatment Options

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## ABSTRACT

Pancreatic neuroendocrine tumors (PNETs) are rare endocrine tumors originating from pancreatic cells, constituting 1-2% of pancreatic tumors. The incidence of PNETs has risen from 0.32 to 0.48 per 100,000 people between 2004 and 2021. Among PNETs, insulinomas are the most common type, characterized by excessive insulin production, with an occurrence rate of 1-4 per million people. This review provides a comprehensive analysis of insulinomas, focusing on their epidemiology, pathophysiology, clinical manifestations, diagnostic methods, and treatment strategies. Insulinomas can be sporadic or associated with Multiple Endocrine Neoplasia Type 1 (MEN-1) syndrome, a genetic disorder caused by mutations in the MEN1 gene. MEN-1-associated insulinomas are often diagnosed earlier and may present as multicentric lesions, whereas sporadic insulinomas are typically solitary and benign. Diagnostic approaches include biochemical tests, such as the 72-hour fasting test, and imaging techniques like CT, MRI, and nuclear medicine scans for tumor localization. Surgical resection remains the primary treatment modality, with high success rates for benign tumors, although emerging techniques like endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) offer

promising alternatives for small, solitary tumors. Medical management, including medications like diazoxide and somatostatin analogs, is crucial for controlling symptoms in patients not amenable to surgery. Prognosis is generally favorable with surgical intervention, but careful monitoring is required for malignant or metastatic disease. Ongoing research is essential to enhance treatment strategies and improve patient outcomes.
**Keywords:** insulinoma, pancreatic neuroendocrine tumors (PNETs), hypoglycemia, surgical resection, diazoxide

## Introduction

Pancreatic neuroendocrine tumors (PNETs) are a rare form of neuroendocrine tumors (NETs) that originate from endocrine cells.Representing 1-2% of all pancreatic tumors, the annual age-adjusted incidence of PNETs has increased from 0.32 per 100,000 people in 2004 to 0.48 per 100,000 people in 2021, according to the Surveillance, Epidemiology, and End Results (SEER) program.[1] Functioning pancreatic neuroendocrine tumors (PNETs) include insulinomas, gastrinomas, VIPomas, glucagonomas, and other types that lead to specific hormonal hypersecretion syndromes. In contrast, non-functioning PNETs constitute the largest category of PNETs; these tumors do not cause hormonal excess syndromes but instead result in morbidity and mortality through local tissue invasion and metastasis. [2] Out of the functioning PNETs insulinoma is the most common one. Insulinomas are uncommon neuroendocrine tumors originating from the pancreatic islet cells, characterized by their capacity to produce and secrete insulin. [3] with the incidence of 1-4 people per million in the general population. [4] The incidence of insulinomas exhibits a distinct age-related peak, occurring most frequently in men during their fifth decade of life and in women during their sixth decade. Additionally, the overall incidence of insulinomas is marginally higher in women compared to men.Over 99% of insulinomas are found within the pancreas, with tumors distributed relatively evenly throughout the organ. Extrapancreatic insulinomas, which are exceptionally rare and may occasionally be metastatic, have been reported in locations such as the lungs, duodenum, ileum, jejunum, splenic hilum, and gastric antrum. Additionally, around 10% of insulinomas are identified as multiple lesions.[2] The purpose of this article is to provide a detailed review of insulinomas, a rare form of pancreatic neuroendocrine tumors (PNETs). It aims to summarize the current understanding of their epidemiology, pathophysiology, clinical manifestations, diagnostic

methods, and treatment options. The article serves as a comprehensive resource for healthcare professionals to improve the diagnosis, management, and outcomes of patients with insulinomas by consolidating existing knowledge on the subject.

## Pathophysiology

Insulinomas may arise either sporadically or as part of Multiple Endocrine Neoplasia Type 1 (MEN-1) syndrome. Historically referred to as Wermer's syndrome, MEN-1 is an autosomal dominant condition linked to mutations in the MEN1 gene located on chromosome 11q13. [5] MEN1 is an autosomal dominant genetic disorder characterized by the occurrence of at least two of the following endocrine conditions: primary hyperparathyroidism, anterior pituitary tumors, and duodenopancreatic neuroendocrine tumors (NETs). The global prevalence of MEN1 is approximately 1 in 30,000, with penetrance increasing with age. By the age of 20, around 75% of patients have developed at least one tumor, with primary hyperparathyroidism or adenoma being the most frequently observed initial manifestation. [6] Insulinomas associated with MEN1 syndrome can present as multiple synchronous or metachronous lesions and are typically identified at an earlier age compared to sporadic cases. This early diagnosis is largely attributed to the implementation of MEN1 screening guidelines. [7] Sporadic insulinomas are generally small, measuring less than 2 cm in diameter in approximately 90% of cases, are usually solitary in 90% of instances, and are benign in about 90% of cases. In contrast, insulinomas associated with MEN-1 syndrome, which affect roughly 4–10% of MEN-1 patients, tend to develop at an earlier age and are often multicentric. The likelihood of recurrence is also higher in individuals with MEN-1 syndrome, with recurrence rates of 21% at 10 and 20 years, compared to 0–5% at 10 years and 0–7% at 20 years in those without the syndrome. [5]

## Symptoms

Most patients present within 1.5 years of symptom onset, although some may experience symptoms for several decades before receiving a diagnosis. [8] The symptoms of insulinoma are caused by the elevated levels of insulin and were first described by Whipple and Frantz in 1935. The Whipple’s triad consist of hypoglycemic symptoms triggered by fasting, circulating glucose levels dropping below 50 mg/dL when symptoms occur and relief of symptoms following glucose administration.[9] Neuroglycopenic symptoms exhibit a broad range and can encompass difficulty awakening, visual disturbances, confusion, lethargy, weakness, unusual

behavior, seizures, loss of consciousness, or coma. Additionally, hypoglycemia triggers catecholamine release and activates the adrenergic sympathetic nervous system, leading to sweating, anxiety, and palpitations. This overlap with psychiatric or neurological symptoms often leads to misdiagnoses, causing delays in identifying the underlying condition.[10] To prevent the onset of symptoms, patients often consume frequent small meals and snacks. [8]

**Diagnosis**

- **Biochemical testing**

  Evaluating an insulinoma involves two critical steps: firstly, confirming the diagnosis through biochemical tests when there is a strong clinical suspicion, and secondly, localizing the tumor. The 72-hour fasting test is regarded as the gold standard for evaluating hypoglycemia, demonstrating a sensitivity of 88.9% and a specificity of 100% for diagnosing insulinoma. [11] It is particularly valuable when the Whipple triad is not evident and when no biochemical tests have been conducted during spontaneous hypoglycemic episodes. A diagnosis is supported by a combination of findings: a plasma glucose concentration below 55 mg/dL, insulin levels greater than or equal to 3 μU/mL, C-peptide levels greater than or equal to 0.6 ng/mL, proinsulin levels greater than or equal to 5 pmol/L, beta-hydroxybutyrate levels less than or equal to 2.7 mmol/L, and a negative sulfonylurea level, all indicating that the hypoglycemia is due to hyperinsulinemia. [12]

- **Radiological findings**

  There are several non-invasive techniques for locating a suspected insulinoma, including transabdominal ultrasound, CT scans, and MRI. Transabdominal ultrasonography has a limited sensitivity for insulinoma localization, ranging from 9% to 64%.[13] In contrast, insulinomas exhibit distinctive features on CT and MRI, with reported sensitivities of 33%-64% and 40%-90%, respectively. CT is currently regarded as the primary method for visualizing insulinomas. CT imaging reveals the precise location of an insulinoma, its relation to adjacent vital structures, and the presence of any metastases. Insulinomas are typically hypervascular, resulting in greater enhancement compared to normal pancreatic tissue during the arterial and capillary phases of contrast administration. Occasionally, insulinomas may present with atypical

CT features, such as hypovascular or hypodense lesions after contrast, hyperdense lesions before contrast, cystic masses, or calcified masses. [4] Magnetic resonance imaging (MRI) is becoming a suitable, safe, and non-invasive alternative with high sensitivity for localizing insulinomas and metastatic disease. Compared to normal pancreatic tissue, β-pancreatic islet cell tumors exhibit low signal intensity on T1-weighted images and increased signal intensity on T2-weighted images. The enhancement pattern, due to the typical hypervascularity of these tumors, is usually homogeneous or ring-enhancing in tumors larger than 2 cm. Metastases follow a similar enhancement pattern. The use of MRI for detecting insulinomas is limited by the typical contraindications to MRI. [8] Another option of imaging is the use of nuclear medicine techiques, such as Ga-68 DOTATATE PET-CT or F-18 FDG PET-CT. [14] 68Ga-DOTATATE has a strong affinity for somatostatin receptor 2, which is often found in neuroendocrine tumors. Prasad et al [15]. reported that up to 80% of insulinomas express somatostatin receptor 2. Additionally, 68Ga-DOTATATE PET/CT scans have been shown to detect neuroendocrine tumors as small as 6 mm. [16] Neuroendocrine tumors (NETs) grow slowly, so 18F-FDG PET/CT is not typically used for their initial evaluation. Early-stage NETs have low metabolic activity and do not show strong uptake on 18F-FDG PET/CT. However, in advanced stages, as the tumors become poorly differentiated, their uptake pattern on 18F-FDG PET/CT changes.[17] In contrast, neuroendocrine tumors show high uptake of 68Ga-DOTATATE due to significant expression of SSR2. 68Ga-DOTATATE PET/CT is more effective than 18F-FDG PET/CT in detecting NETs because of its higher sensitivity in identifying low-grade tumors.[17, 18]

**Surgical Management of Insulinoma**

Surgical resection remains the gold standard for the treatment of insulinomas, demonstrating success in over 95% of cases. This high success rate is attributed to the typically benign nature of insulinomas (malignancy rate remains below 10%), their usually solitary presentation except in patients with Multiple Endocrine Neoplasia type 1 (MEN1), and the efficacy of preoperative localization using conventional imaging modalities [19]. The primary goal of surgery is to achieve complete resection of all macroscopic lesions. Mesenteric artery invasion precludes surgical intervention. In metastatic situations, palliative liver surgery is considered when more than 90-95% of the macroscopic tumor mass can be excised or when symptom control is

inadequate. For severe hypoglycemia, a less extensive resection of 60-70% of liver metastases might be considered, though the benefits of this approach remain uncertain. Surgical mortality should remain below 5%, even in cases of metastatic disease [20].

The type of surgical resection is determined by the tumor's location and its proximity to the main pancreatic duct [21]. The following surgical techniques are typically employed:

- **Distal Pancreatectomy:** This procedure involves the resection of the pancreas at the level of the isthmus.
- **Caudal Pancreatectomy:** Known for its parenchyma-sparing approach, this technique involves resection pancreatic tissue on the left side of the isthmus.
- **Enucleation and Parenchyma-Sparing Pancreatectomy:** This category includes central pancreatectomy, caudal pancreatectomy and resection of the uncinate process, all recommended whenever feasible [21].

When preoperative localization of the tumor is achieved, enucleation or pancreatic resection can be performed using minimally invasive techniques, reducing the overall impact on the patient. For non-localized tumors in sporadic insulinoma cases, surgical exploration is warranted to ensure thorough treatment. Despite significant advancements in laparoscopic surgery, open surgery remains the most accepted method for insulinoma resection. Intraoperative palpation of the pancreas, in conjunction with intraoperative ultrasound (IOUS), enables the detection of over 80% of tumors. However, about 10% of insulinomas are neither palpable nor detectable without the assistance of IOUS. Enucleation is the preferred procedure for small (<2.5 cm), unilocular, benign, superficial insulinomas situated more than 2-3 mm away from the main pancreatic duct and major blood vessels. Routine lymph node dissection is not indicated for benign neoplasms but is mandatory for malignant tumors to ensure comprehensive treatment [8].

Throughout the surgical procedure, blood glucose levels should be closely monitored at 15-minute intervals to detect any signs of intraoperative hypoglycemia. Intravenous dextrose infusion can be discontinued once the tumor is excised, with continued vigilant monitoring of blood glucose levels postoperatively to prevent complications [21].

## Postoperative Management and Complications

In the postoperative phase, frequent monitoring for hypoglycemia is crucial. Patients often experience transient rebound hyperglycemia, which can be controlled without the need for extra insulin administration. Potential postoperative complications from pancreatic surgery include the formation of pancreatitis, intra-abdominal abscesses, pseudocysts, pancreatic fistulas and the development of diabetes. These complications require careful monitoring and management to ensure patient recovery and long-term health [21]

## Endoscopic Ultrasound-Guided Radiofrequency Ablation (EUS-RFA)

Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) is emerging as a minimally invasive option with the prospect to replace surgery as the first-line treatment for benign, solitary, sporadic and small (<2 cm) insulinomas. Conducted under real-time guidance, EUS-RFA offers immense precision, safety, and predictability, and is characterized by an acceptable safety profile. Currently, this technique is frequently employed for patients who are high-risk or otherwise inoperable. However, there is a pressing need for a randomized controlled trial to firmly establish the role of EUS-RFA in the therapeutic algorithm for managing insulinomas [22].

## Medical Management

While surgery is the definitive treatment for insulinomas, medical management aimed at normalizing blood glucose levels is essential for patients experiencing symptomatic hypoglycemia prior to surgery or when surgical intervention is not feasible [20].

## Dietary Management

For dietary management, patients are advised to consume regular meals or snacks that are rich in slow-digesting carbohydrates. A bedtime or late-night meal is generally sufficient for most patients, though nocturnal tube feeding may be necessary to prevent nocturnal hypoglycemia in those who are severely symptomatic. In cases of severe recurrent hypoglycemia, intravenous glucose administered via a central IV catheter might be needed. Additionally, a continuous glucose monitoring system can assist patients in detecting hypoglycemic events, thereby helping to prevent severe complications, especially during the nighttime [7].

## Pharmacological Treatment

### Diazoxide

Diazoxide remains the reference medication for treating insulinomas, though it is not universally effective and can have several adverse effects. Diazoxide functions by attaching to the sulfonylurea receptor-1 subunit of the ATP-sensitive K+ (KATP) channel, which opens the channel and enhances its permeability to potassium ions. This action hyperpolarizes the beta cells, thereby inhibiting Ca2+-dependent insulin release. [23] As a benzothiadiazide, diazoxide directly inhibits insulin release and is generally the initial drug used, controlling hypoglycemia in 50-60% of patients. Some insulinoma patients have benefited from diazoxide for over 20 years. Typical doses range between 300 and 900 mg per day, divided into three doses. Common dose-limiting side effects include fluid retention, edema, nausea, palpitations, anorexia and hirsutism in women undergoing treatment. Combining diazoxide with a thiazide diuretic is typically recommended to prevent edema, fluid retention, and severe weight gain [7].

### Somatostatin Analogs

Somatostatin analogs (SRLs) offer a second-line treatment option. These medications are well-tolerated and rapid-acting, functioning through the SST2 and SST5 receptors to control insulin secretion in tumors [20]. While expression of SSTR2 and SSTR5 is usually low in indolent insulinomas, it is typically high in aggressive forms. First-generation SRLs, such as octreotide and lanreotide, which have high affinity for SSTR2, can effectively suppress pathological insulin hypersecretion in patients with SSTR2-expressing insulinomas. The long-acting somatostatin analogue, lanreotide Autogel, is approved as the first-line therapy for managing tumor growth in low-grade (G1-2) pancreatic neuroendocrine tumors (panNET). A preliminary challenge with the short-acting octreotide is generally recommended before transitioning to a long-acting formulation, to avoid paradoxical hypoglycemia due to suppression of counter-regulatory glucagon secretion in tumors lacking SSTR2 expression. The most commonly experienced side effects included abdominal pain and diarrhea. [24]

### Everolimus

Everolimus, an mTOR inhibitor, has shown efficacy in controlling hypoglycemia in patients with malignant insulinomas or those unable to undergo surgical resection [19]. By inhibiting the Pi3K/AKT/mTOR pathway, everolimus has demonstrated antitumor effects in pancreatic

NETs in multiple phase II and III trials. The drug's side effects, such as hyperglycemia and hypertriglyceridemia, are leveraged for insulinoma treatment. Everolimus may inhibit insulin secretion and reduce beta-cell count, although its toxicity places it as a third-line treatment after the failure or intolerance of diazoxide and somatostatin analogs. Common side effects include aphthae, diarrhea, fatigue, hypophosphatemia, and interstitial pneumopathy, necessitating tailored follow-up [20].

**Other Novel Treatments**

Other effective methods for controlling hypoglycemia in insulinoma patients where complete surgical resection is not possible include ethanol ablation of the tumor, peptide receptor radionuclide therapy (PRRT) using radiolabeled somatostatin analogs, irreversible electroporation (IRE) and image-guided robotic radiosurgery. [19, 8].

**Prognostic Factors**

About 90-95% of insulinomas are benign, and patients have a 5-year survival rate of up to 95-100% following surgical resection. Recurrence rates are reported to be between 3-5.4%, with metastatic disease potentially developing several years post-resection, especially in grade G2 tumors [8]. Pathologic classification into well-differentiated tumors or poorly-differentiated carcinomas is crucial for prognosis. Malignant insulinomas are usually well-differentiated, with liver metastasis being a major prognostic determinant. The impact of lymph node metastasis on prognosis is well-documented for pancreatic neuroendocrine tumors (NETs). At the metastatic stage, the initial evaluation should determine tumor volume, monitor progression through successive assessments, assess the proliferation index, and consider comorbidities. Poor prognostic factors include persistent hypoglycemia, a liver tumor burden surpassing 30% of the liver's total volume, ongoing morphological progression, and a Ki67 index above 10-20%.[20].

**Summary**

**Introduction and Purpose**

Pancreatic neuroendocrine tumors (PNETs) are rare tumors originating from endocrine cells in the pancreas, accounting for 1-2% of pancreatic tumors. The incidence of PNETs has risen from 0.32 to 0.48 per 100,000 people from 2004 to 2021. Among PNETs, insulinomas are the most common functioning type, characterized by insulin overproduction and occurring at a rate of 1-

4 per million people. This article aims to review insulinomas, focusing on their epidemiology, pathophysiology, clinical features, diagnostic approaches, and treatment options. It serves as a comprehensive resource to enhance the understanding and management of insulinomas for healthcare professionals.

**State of Knowledge**

Insulinomas may develop sporadically or as a component of Multiple Endocrine Neoplasia Type 1 (MEN-1) syndrome. MEN-1 is a genetic disorder linked to mutations in the MEN1 gene and presents with endocrine conditions such as hyperparathyroidism and pancreatic neuroendocrine tumors. While sporadic insulinomas are usually small, solitary, and benign, those associated with MEN-1 are often multicentric and diagnosed earlier due to screening practices. Diagnostic methods include biochemical tests, with the 72-hour fasting test being the gold standard, and imaging techniques like CT, MRI, and nuclear medicine scans for tumor localization. Surgical resection remains the primary treatment, with success rates exceeding 95% for benign tumors. Alternatives like endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) are emerging for small, solitary tumors.

**Summary (Conclusions)**

Insulinomas are uncommon but important due to their ability to significantly impact a patient's health. Early and accurate diagnosis is essential, utilizing biochemical tests and advanced imaging techniques. Surgical resection is the gold standard for treatment, achieving high success rates due to the typically benign nature of these tumors. Emerging techniques such as EUS-RFA offer promising alternatives for small, inoperable tumors. Medical management, including drugs like diazoxide and somatostatin analogs, plays a crucial role in controlling symptoms and managing patients who are not surgical candidates. Prognosis is generally favorable with surgical intervention, but careful monitoring is necessary, particularly for those with malignant or metastatic disease. Continued research and development in treatment strategies are essential for improving patient outcomes.

**Disclosure:**

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