International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	INSULINOMA: CONTEMPORARY STRATEGIES FOR DIAGNOSIS, CLINICAL PRESENTATION, AND MULTIMODAL TREATMENT OF PANCREATIC NEUROENDOCRINE INSULIN-SECRETING TUMORS
ARTICLE INFO	Konrad Strużek, Agnieszka Kwiatkowska, Ewelina Mączka, Wiktor Tracz, Patrycja Świercz, Kinga Teper, Sandra Khiralla-Gawlik, Aleksandra Anna Strzelecka, Aleksandra Ewa Basak. (2025) Insulinoma: Contemporary Strategies for Diagnosis, Clinical Presentation, and Multimodal Treatment of Pancreatic Neuroendocrine Insulin-Secreting Tumors. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3659
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3659
RECEIVED	28 July 2025
ACCEPTED	02 September 2025
PUBLISHED	11 September 2025
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INSULINOMA: CONTEMPORARY STRATEGIES FOR DIAGNOSIS, CLINICAL PRESENTATION, AND MULTIMODAL TREATMENT OF PANCREATIC NEUROENDOCRINE INSULIN-SECRETING TUMORS

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ABSTRACT

Introduction: Insulinoma, though rare, represents the most frequent hormonally active neuroendocrine neoplasm of the pancreas, responsible for causing endogenous hypoglycemia. In over 90% of cases, it presents as a solitary, benign, well-defined tumor smaller than 2 cm. Despite the presence of typical clinical signs, diagnosis is often postponed due to nonspecific symptoms that may mimic neurological or psychiatric disorders.
Objective: This review aims to provide an updated overview of diagnostic strategies and treatment options for insulinomas in adults, excluding those linked to MEN syndrome or von Hippel-Lindau disease, with particular focus on imaging modalities for tumor localization and therapeutic alternatives for unresectable or malignant lesions.
Methods: We analyzed the effectiveness of various imaging techniques, including non-invasive modalities (ultrasound, CT, MRI) and invasive methods (endoscopic ultrasound [EUS], arterial stimulation with venous sampling [ASVS]), in detecting insulinomas. Surgical approaches were reviewed alongside minimally invasive options such as alcohol ablation, radiofrequency ablation (RFA), embolization, and medical therapies. Management strategies for malignant insulinomas were also examined, emphasizing the role of multimodal treatment, including chemoembolization and liver transplantation.
Conclusions: Surgical removal remains the preferred treatment for most insulinomas, offering the possibility of complete remission. Precise preoperative localization greatly enhances surgical success and minimizes complications. In cases where resection is not feasible or in malignant disease, alternative therapies can help manage hypoglycemia and improve quality of life. Progress in imaging techniques and glucose monitoring is reshaping the diagnostic and therapeutic landscape for insulinoma.

KEYWORDS

Insulinoma, Hypoglycemia, Imaging Diagnostics, EUS, ASVS, Surgical Treatment, Octreotide

CITATION

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Introduction.

Insulinomas are the most common hormonally active endocrine tumors of the pancreas.[1, 2, 3, 4] These are insulin-secreting pancreatic tumors that lead to hypoglycemia.[5, 6, 7] Insulinoma is diagnosed in 1–4 individuals per million in the general population and accounts for 1%–2% of all pancreatic neoplasms.[8, 9, 10] It can occur at any age and affects men and women equally. According to reports, up to 90% of insulinomas are benign, 90% are solitary tumors, over 90% are located within the pancreas, and 90% of them are smaller than 2 cm in diameter. [10, 11, 12, 13]

Insulinomas are evenly distributed throughout the pancreas. Most are located within or directly adjacent to pancreatic tissue. Extraparenchymal insulinomas that cause hypoglycemia are extremely rare, occurring in fewer than 2% of cases. The most common extrapancreatic location is the duodenal wall.[8] The causes and mechanisms of insulinoma development remain unknown.

Once the presence of insulinoma is confirmed through biological and biochemical testing, preoperative tumor localization is typically performed using computed tomography (CT).[14, 15, 16] Additional methods include magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), [16–22] and selective arterial calcium stimulation with hepatic venous sampling (ASVS), as well as angiography with arterial stimulation and venous sampling. [23–28]

Surgical resection is the primary treatment for insulinoma, making precise tumor localization—either before or during surgery—critically important. During the procedure, an experienced surgeon can often locate the tumor using manual palpation of the pancreas combined with intraoperative ultrasound. These techniques are highly sensitive for detecting insulinomas, supporting the view of some surgeons that preoperative localization may not always be necessary. [29–33]

This review presents selected recent findings on the clinical diagnosis and treatment of insulinomas in adults not associated with multiple endocrine neoplasia (MEN) syndrome or von Hippel-Lindau disease.

Historical Background

In 1869, while still a medical student, Paul Langerhans was the first to describe the cells of the pancreatic islets. Several decades later, in 1922, Banting and Best isolated insulin—originally referred to as”isletin”—from an extract of a dog’s pancreas. In 1923, Harris proposed that hyperinsulinism could represent a clinical issue, contrasting it with the hypoinsulinism seen in diabetes.[34] His hypothesis was confirmed a year later, when numerous case reports were published describing patients with symptoms of hyperinsulinism.[34]

It was not until three years later that Wilder and his colleagues first established a connection between hyperinsulinism and a functional islet cell tumor. They made this discovery during surgery on a patient suffering from hypoglycemia, during which a metastatic islet cell carcinoma was found in the liver. The first surgical removal of an islet cell tumor was performed by Graham in 1929.[34]

A few years later, Whipple observed that hypoglycemic symptoms were triggered by fasting and that, when they occurred, blood glucose levels fell below 50 mg/100 ml. He also noted that the symptoms resolved after glucose administration, laying the foundation for the diagnosis of insulinoma. This led to the formulation of the so-called”Whipple's triad, " which remains a diagnostic standard to this day.[34]

Clinical Symptoms

Insulinomas are the most common cause of hypoglycemia resulting from endogenous hyperinsulinism. The episodic nature of hypoglycemic attacks stems from the periodic secretion of insulin by the tumor.[8] Typical autonomic symptoms associated with insulinoma include excessive sweating, tremors, and palpitations. In contrast, neuroglycopenic symptoms may involve confusion, behavioral changes, personality alterations, visual disturbances, seizures, and coma.[35, 36]

Diagnosing insulinoma can be challenging. Although it was previously believed that symptoms occurred only during fasting or after physical exertion, it is now known that patients with insulinoma may also experience symptoms after meals.[37, 38] The classical diagnosis of insulinoma is based on meeting the criteria of Whipple’s triad, which remains a cornerstone in the diagnostic process. The triad includes:

(1) hypoglycemia, defined as a plasma glucose concentration below 50 mg/dL;

(2) neuroglycopenic symptoms; and

(3) rapid resolution of symptoms following glucose administration (see Table 1).[39]

Table 1. Diagnosis of insulinoma

Classical diagnosis
Hypoglycemia (plasma glucose < 50 mg/dL)
Neuroglycopenic symptoms
Prompt relief of symptoms following the administration of glucose
Present consensus
At the time of hypoglycemia during a 72-h fasting test:
5 mIU/L (36 pmol/L) insulin threshold
0.6 ng/mL (0.2 nmol/L) C-peptide threshold
Insulin/C-peptide ratio < 1.0
20 pmol/L proinsulin cut-off level
Absence of sulfonylurea (metabolites) in the plasma or urine

In adult patients with neuroglycopenic symptoms or confirmed low blood glucose levels, the gold standard for biochemical diagnosis is the measurement of plasma glucose, insulin, C-peptide, and proinsulin levels during a 72-hour supervised fast (Table 1). This prolonged fasting test can detect up to 99% of insulinoma cases.[40]

Endogenous hypoglycemia caused by insulinoma was historically diagnosed based on abnormal levels of insulin and C-peptide, and more recently, proinsulin during fasting-induced hypoglycemia. There is now a general consensus regarding threshold values that must be exceeded for insulin, C-peptide, and proinsulin levels to be considered abnormal. In the past, diagnostic indices were used based on insulin-to-glucose ratios, with an insulin-to-C-peptide ratio of less than 1.0 being typical in confirmed insulinoma cases.[41, 42]

Importantly, a normal insulin level does not exclude the diagnosis, as not all patients with insulinoma exhibit elevated insulin. Additionally, since insulinoma cells typically secrete more proinsulin than normal β-cells, elevated proinsulin levels are recognized as a diagnostic clue, independent of concurrent blood glucose levels.[43] The introduction of proinsulin testing has allowed serum proinsulin thresholds to be used as a diagnostic tool. A proinsulin level of at least 20 pmol/L during hypoglycemia (with glucose <45 mg/dL) is considered indicative of insulinoma (Table 1).[43, 44, 45]

Delays in diagnosing insulinoma are relatively common, as symptoms often occur before the tumor is actually identified. Symptoms are frequently misattributed to psychiatric, cardiac, or neurological disorders, complicating accurate diagnosis.[46] Once insulinoma is suspected, it is essential that patients receive prompt and safe treatment. Generally, surgical resection of the tumor is an effective cure for insulinoma patients.

However, the necessity of preoperative tumor localization and the selection of diagnostic modalities remain topics of debate. In the past, confirmation of Whipple's triad—(1) symptoms caused or likely caused by hypoglycemia, (2) low plasma glucose measured during symptoms, and (3) resolution of symptoms after glucose normalization—often led to immediate referral for surgery.[47, 48] Today, there is widespread agreement that preoperative localization of the tumor is highly beneficial. It helps determine whether enucleation or pancreatic resection is required and whether a minimally invasive laparoscopic approach is feasible. Accurate preoperative localization also shortens the duration of surgery, reducing the risk of complications and perioperative mortality.[27]

It is worth noting that most tumors are located within the pancreas, with 90% being solitary lesions, 90% measuring less than 2 cm in diameter, and with even distribution throughout the head, body, and tail of the pancreas.

Non-Invasive Imaging

Several non-invasive methods are available for detecting suspected insulinomas, including transabdominal ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI). However, the effectiveness of transabdominal ultrasound in detecting insulinomas is limited, with sensitivity ranging from 9% to 64%.[49] Despite this, insulinomas often exhibit characteristic imaging features on both CT and MRI, with reported detection rates of 33%–64% for CT and 40%–90% for MRI, respectively.[10, 50] MRI generally outperforms CT in terms of sensitivity and specificity and is particularly effective in identifying extrapancreatic lesions.[16]

CT is a safe and widely accessible diagnostic tool, and its effectiveness is not dependent on operator expertise. It allows for precise localization of the insulinoma, assessment of its relationship to vital anatomical structures, and detection of potential metastases.[50] Insulinomas are typically hypervascularized tumors, exhibiting stronger enhancement than normal pancreatic tissue during the arterial and capillary phases after contrast administration.[16] However, insulinomas may sometimes present atypically on CT, showing hypoenhancing lesions with low attenuation after contrast, hyperdense areas on pre-contrast images, or cystic or calcified masses.[16] When calcification is present, it usually appears as small, nodular foci and is more frequently observed in malignant than benign tumors.[51, 52]

Thanks to technological advancements, the quality of CT imaging has improved significantly. One recent study demonstrated that multidetector CT was able to visualize 94.4% of insulinoma cases. Currently, CT is considered the preferred first-line diagnostic method for detecting these tumors.[53]

Recent studies provide strong evidence for the effectiveness of MRI in imaging insulinomas, and researchers have confirmed the high sensitivity of this method in their detection.[16, 50] Like CT, magnetic resonance imaging is a safe, non-invasive, and rapid technique that also aids in identifying metastases. Insulinomas typically appear as low-signal areas on T1-weighted images and high-signal areas on T2-weighted images.[51]

Nevertheless, the use of MRI in insulinoma diagnostics does have some limitations, mainly due to standard contraindications to the procedure. However, modern MRI systems allow for rapid breath-hold, triphasic T1-weighted sequences with dynamic gadolinium enhancement and/or diffusion-weighted imaging (DWI).[19, 50]

These advanced sequences significantly reduce motion artifacts, enabling precise evaluation of the pancreas during both the arterial and venous phases. MRI offers all the advantages of CT, and recent studies suggest that it may actually be a more sensitive diagnostic tool. Currently, MRI is used as a second-line modality for localizing insulinomas, but it may replace CT in the future as its availability increases and clinical expertise advances.[50]

Invasive Diagnostic Methods

The diagnostic process for insulinoma typically begins with standard endocrinological testing, with particular emphasis on the prolonged fasting test. Once a diagnosis of insulinoma is confirmed, non-invasive imaging techniques are employed to localize the source of excessive insulin secretion. However, invasive methods such as endoscopic ultrasound (EUS) and selective arterial calcium stimulation with hepatic venous sampling (ASVS) have been shown to be highly effective for preoperative tumor localization, often outperforming non-invasive techniques in terms of accuracy.[20]

EUS is currently the preferred diagnostic method in many Western centers, with reported detection rates for insulinomas ranging from 86.6% to 92.3%.[10, 47] Insulinomas typically appear on EUS as homogeneous, hypoechoic, round, and well-demarcated lesions. Despite its high efficacy, EUS has certain limitations. It can result in both false positives and false negatives, and its diagnostic accuracy heavily depends on the experience of the operator.[22]

Some insulinomas may go undetected during preoperative EUS if they are entirely isoechoic. Factors such as low body mass index, female sex, and younger age are associated with an increased risk of false-negative imaging results.[20] Additionally, the sensitivity of EUS is influenced by the location and size of the tumor—it is highest for tumors located in the head of the pancreas, and lowest for those in the tail or outside the pancreas.[10]

Once the tumor is localized, fine-needle aspiration (FNA) of the pancreas can be performed for preoperative confirmation of insulinoma. The advancement of EUS-guided techniques has made EUS-FNA particularly effective, especially since most functional tumors are small in size. EUS-guided FNA is gaining popularity and is likely to become a standard method for the diagnosis and staging of pancreatic tumors.[9]

Undoubtedly, angiography combined with ASVS should not be performed before utilizing non-invasive methods such as CT or MRI. Nevertheless, it remains an exceptionally sensitive technique for the precise localization of insulinomas and often provides more detailed information than EUS.[27] While anatomical imaging techniques cannot assess the hormonal activity of a tumor, ASVS allows for functional localization by confirming hormonal activity in specific regions.

The use of ASVS (Arterial Stimulation with Venous Sampling) allows for more precise surgical planning and may reduce the risk of requiring repeat surgery.[24] In atypical cases of insulinoma, preoperative localization using ASVS is crucial. The reported accuracy of this method in tumor identification ranges from 94% to 100%.[23, 28]

In ASVS studies, insulinomas appear as well-defined, round or oval vascular lesions that demonstrate greater vascularity than the surrounding healthy pancreatic parenchyma. These lesions are typically visible in the early arterial phase and may persist variably during the venous phase. Localization of insulinomas with ASVS is based on the principle that injection of hyperosmolar calcium into arteries supplying the tumor induces degranulation of tumor cells and the release of insulin into the portal venous system, resulting in a measurable increase in insulin levels in hepatic venous blood samples.[27]

During ASVS, the most commonly evaluated arteries are the splenic artery, gastroduodenal artery, superior mesenteric artery, and the proper hepatic artery. An increase in insulin levels in the hepatic vein following calcium injection indicates tumor location as follows:

- Body or tail of the pancreas (splenic artery),
- Anterior head of the pancreas (gastroduodenal artery),
- Posteroinferior head of the pancreas (superior mesenteric artery).

If an insulin spike occurs following injection into the proper hepatic artery, it may suggest hepatic metastases. The time-course analysis of insulin concentration changes after calcium injection reveals that significant elevations occur only in vessels supplying the insulinoma.

With the wide array of imaging techniques now available, it is possible to achieve accurate localization of insulinomas both preoperatively and intraoperatively, helping to avoid so-called blind pancreatic resections.[54] An experienced surgeon can often localize the tumor effectively using manual palpation of the pancreas and intraoperative ultrasound, both of which demonstrate high sensitivity.[29, 30, 31] These methods show clinically acceptable sensitivity, ranging from 75% to 95% for palpation and 80% to 100% for intraoperative ultrasound.[29, 32, 55]

Treatment of Benign Insulinomas

Although the majority of benign insulinomas can be effectively cured through surgical resection, several alternative therapeutic options are available, including octreotide injections, alcohol ablation under EUS guidance, radiofrequency ablation (RFA), and embolization of the pancreatic tumor.[56–62]

Once the insulinoma has been localized, surgical treatment is recommended. The type of surgery depends on the tumor's characteristics, such as type, size, and location. Organ-sparing procedures such as enucleation, partial pancreatectomy, or central pancreatectomy are often preferred to preserve as much pancreatic tissue as possible, thereby minimizing the risk of long-term exocrine or endocrine insufficiency.[63]

Laparoscopic resection has commonly been used for benign, small-sized insulinomas located in the body or tail of the pancreas.[64] In contrast, radical resection should be considered in cases where the tumor is multiple, poorly circumscribed, larger than 4 cm, or involves or lies close to the main pancreatic duct. Lymphadenectomy is usually not performed.

Although the cure rate after surgical resection of insulinoma is very high, the risk of postoperative complications must be considered—particularly the development of pancreatic fistula.[65–67]

Surgical treatment of insulinomas, however, carries a significant risk of complications and mortality, making it unsuitable for patients with high surgical risk. As an alternative, minimally invasive techniques such as alcohol ablationand radiofrequency ablation (RFA) have been successfully used in the treatment of both primary liver tumors and hepatic metastases. Recently, successful cases of EUS-guided alcohol ablation and CT-guided RFA of pancreatic insulinomas have been reported.[57, 58]

In both cases, the patients were in poor general condition and experienced recurrent episodes of hypoglycemia. Surgical resection of the benign pancreatic insulinoma was deemed unfeasible, so ablation of the solitary tumor was performed instead. Both patients were discharged without complications and did not experience further hypoglycemic episodes.

Another non-surgical therapeutic option is embolization of the pancreatic insulinoma.[56, 68, 69] Since insulinomas typically appear as hypervascular lesions during the arterial phase of angiography, embolization can be flow-directed, allowing embolic particles to target only the tumor.

Although there is ongoing debate as to whether these methods can be considered definitive treatments, they may be considered viable alternatives for patients who are not surgical candidates—for example, due to advanced age, poor general health, multiple previous abdominal surgeries, high surgical risk, or personal refusal of operative intervention.

Insulinomas are rare endocrine tumors, most of which can be effectively removed surgically. Pharmacological treatment aimed at stabilizing blood glucose levels plays an important role in preoperative management and also serves as an option for patients who are not candidates for surgery—for example, in cases of diffuse β-cell disease, multiple tumors, inoperable malignant insulinomas, surgical contraindications, or refusal of surgical treatment.[60]

Octreotide, a somatostatin analog, works by activating somatostatin receptor subtype 2 (sst2), thereby inhibiting insulin secretion and the activity of various gastrointestinal hormones. This drug has been successfully used in the treatment of insulinomas, effectively stabilizing blood glucose levels.[61, 62] In addition, octreotide has antiproliferative properties and shows moderate antitumor effects against pancreatic neuroendocrine tumors.[70]

Treatment may begin with short-acting octreotide, administered 2–4 times daily, or with long-acting formulations at doses of 20–30 mg every four weeks.[71] Starting therapy with short-acting octreotide allows for the assessment of patient tolerance, particularly with regard to potential gastrointestinal side effects.

As such, somatostatin analog therapy represents a practical, non-surgical option for controlling hypoglycemia and managing insulinomas.[72]

Medical Treatment of Malignant Insulinoma

An insulinoma is classified as malignant only when there is local invasion into adjacent soft tissues or when metastases to lymph nodes or the liver have been confirmed.[73] According to reports, malignant insulinomas account for 7% to 10% of all cases, with a 10-year survival rate of approximately 29%.[2, 73–75] The most common sites of metastasis or recurrence are the liver and regional lymph nodes.

Aggressive surgical treatment is recommended, as these tumors tend to have lower malignancy potential compared to exocrine ductal carcinomas and are often associated with challenging hormonal symptoms. Radiofrequency ablation (RFA) may be used to reduce tumor burden in the liver and alleviate hormonal symptoms.[59, 76]

Selective embolization, either alone or in combination with intra-arterial chemotherapy, is a recognized approach to reducing both hormonal manifestations and hepatic metastatic load. Although clinical experience is limited, liver transplantation may be considered in selected patients with extensive hepatic metastases and no extrahepatic disease.

A multimodal, intensive, staged therapeutic approach—including chemoembolization, RFA, liver resection, and transplantation—can prolong survival in patients with sporadic malignant insulinoma, even in the presence of liver metastases.[77, 78]

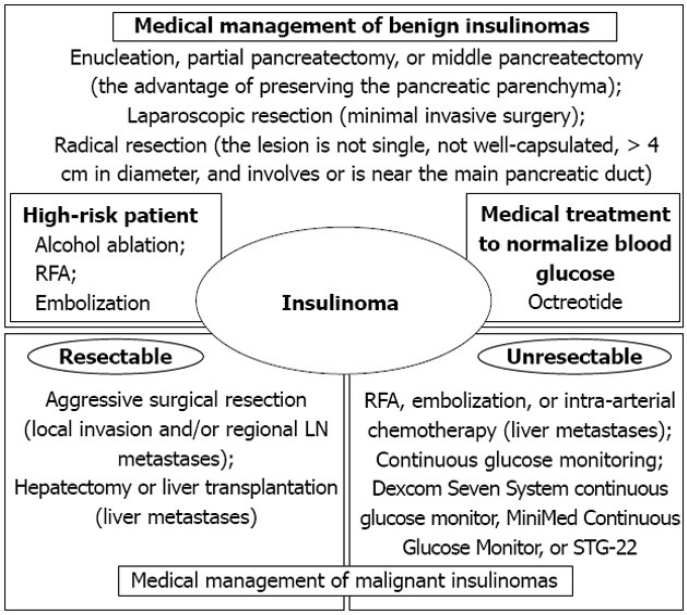
Malignant insulinomas remain exceptionally rare tumors. In many patients, these tumors are unresectable, and pharmacological options are limited in their ability to effectively prevent hypoglycemic episodes. Continuous glucose monitoring (CGM) can aid in detecting hypoglycemia, evaluating treatment efficacy, and confirming remission following surgical intervention. The literature describes the use of CGM systems such as Dexcom Seven (Dexcom, San Diego, USA) and MiniMed CGM (Medtronic MiniMed, Northridge, USA).[79, 80]

Studies have shown that CGM is a valuable adjunct to therapy, helping prevent hypoglycemic episodes by alerting patients to falling blood glucose levels before neuroglycopenic symptoms appear. It is essential, however, that patients respond immediately by ingesting glucose upon detection of hypoglycemia by the device.

In more critically ill patients with inoperable malignant insulinomas and difficult-to-control hypoglycemia, the STG-22 system (Nikkiso Co., Tokyo, Japan) is recommended for blood glucose monitoring. This device has proven to be reliable and accurate, with results comparable to those of the ABL 800FLEX analyzer (Radiometer Medical ApS, Brønshøj, Denmark), which is endorsed by the National Committee for Clinical Laboratory Standards.[81, 82]

The STG-22 closed-loop glucose control system includes a sensor for detecting and/or monitoring glucose levels and pumps that automatically deliver the appropriate doses of insulin or glucose. The pumps are computer-controlled, operating based on a predefined target blood glucose level set prior to system activation.[83, 84]

Clinical studies have confirmed that the STG-22 system is safe and effective in maintaining proper glycemic control in surgical patients, while also preventing hypoglycemic episodes.[85–87] *(See Figure 1)*



Glycemic control in patients with insulinoma

Surgical treatment, which offers the possibility of a complete cure, is still considered the method of choice. Its effectiveness in reducing symptoms is estimated at over 95%. In the perioperative period, and in situations where insulinoma is not eligible for surgery or the procedure is contraindicated, effective management of potentially dangerous hypoglycemic episodes is crucial. [87] Difficult-to-control hypoglycemia poses a significant problem in patients with malignant insulinomas, as the progressive growth of the tumor significantly complicates the treatment of severe hypoglycemic episodes. Due to the life-threatening nature of the tumor's hormonal activity, symptom control remains a key element of therapy. [88] Approaches used in the prevention and treatment of hypoglycemia include patient and caregiver education, lifestyle modifications, pharmacological treatment, therapies aimed at tumor mass reduction, as well as the use of continuous glucose monitoring systems. [89, Figure 2]

Table 1. Methods of management of insulinoma associated hypoglycemia. TAE - trans-arterial embolization, TACE - trans-arterial chemoembolization, SIRT - selective internal radiation therapy, PRRT - peptide receptor radionuclide therapy

Management of insulinoma associated hypoglycemia	
In all patients	
Education of patient and his/her relatives (recognition and reacting to hypoglycemic symptoms)	
Lifestyle modification (frequent meals rich in complex carbohydrates at regular intervals, avoiding driving and excessive exercise)	
Treatment of hypoglycemia	
Mild hypoglycemia/conscious patients: 15 to 20 grams of glucose or fast-acting carbohydrate meal/drink every 15 minutes until restoration of euglycemia, subsequent ingestion of meal rich in complex carbohydrates	
Severe hypoglycemia/unconscious patients: 25 gram boluses of 50% glucose every 15 minutes until restoration of euglycemia; in the event of lack of IV access, 1 mg of glucagon i.m. or s.c.	
Recurrent hypoglycemia: IV infusion of 10% or 20% glucose or enteral nocturnal feeding	
Prevention of hypoglycemia	
Benign tumors	**Malignant tumors**
• Diazoxide – 3-8 mg/kg/day in 2-3 doses (start with 150-200 mg, increase to appropriate dose) • Somatostatin analogs: - consider using somatostatin receptor scintigraphy to choose patients who will benefit most - start with short-acting s.c. form of octreotide 100-600 µg/day in 2-4 doses for 2 weeks, continue for 2 weeks after the first dose of long-acting form (start with 100-200 µg, increase to appropriate dose; observe in hospital) - if response is appropriate, consider long-acting forms: octreotide 20-30 mg i.m. every 4 weeks *or* lanreotide 30 mg i.m. every 2 weeks *or* lanreotide 60-120 mg s.c. every 4 weeks	• Somatostatin analogs: - consider using somatostatin receptor scintigraphy to choose patients who will benefit most - start with short-acting s.c. form of octreotide 100-600 µg/day in 2-4 doses for 2 weeks, continue for 2 weeks after the first dose of long-acting form (start with 100-200 µg, increase to appropriate dose; observe in hospital) - if response is appropriate, use long-acting forms: octreotide 20-30 mg i.m. every 4 weeks *or* lanreotide 30 mg i.m. every 2 weeks *or* lanreotide 60-120 mg s.c. every 4 weeks • Everolimus – 10 mg/day - if not well tolerated – use 5 mg/day - if loss of response – consider discontinuation and re-administration
Aim for treatment of choice – surgery	Consider cytoreductive methods – debulking surgery, liver metastases cytoreductive therapies (TAE, TACE, SIRT), chemotherapy and PRRT
In case of problems in maintaining blood glucose levels – consider use of continuous glucose monitoring systems. In rare cases of inefficiency of standard pharmacotherapy and other techniques for hypoglycemia management – carefully consider use of other hypoglycemic drugs – glucocorticoids, beta blockers, phenytoin or calcium channel inhibitors.	

Conclusions

Insulinomas are the most common pancreatic neuroendocrine tumors and are responsible for hypoglycemia caused by endogenous insulin overproduction. More than 90% of cases involve solitary, well-circumscribed, and benign lesions of small size. Surgical resection is the treatment of choice and represents the only curative option. In most cases, insulinomas can be localized intraoperatively by an experienced surgeon.

But what should be done when the tumor cannot be identified during surgery? Based on the reviewed data, a multimodal imaging strategy—including both non-invasive and invasive techniques—is recommended when standard diagnostic methods fail. Blind pancreatic resections in patients with insulinoma-induced hypoglycemia should be strictly avoided.

Accurate tumor localization allows for efficient surgical planning, reduces operative time, minimizes the need for repeat procedures, and decreases the rate of perioperative complications—factors that, in most cases, lead to successful treatment outcomes.[39]

In cases of malignant insulinoma, an aggressive surgical approach should be considered, including extensive pancreatic resection, hepatic metastasectomy, and in some instances liver transplantation, if technically feasible, to improve prognosis. Additionally, in the presence of hepatic metastases, intensive adjunct therapies such as chemoembolization or radiofrequency ablation (RFA) may be used to control hypoglycemic symptoms.

For patients with unresectable or uncontrolled malignant pancreatic insulinomas, a multimodal therapeutic strategyshould be employed—not only to reduce hypoglycemic episodes but also to improve quality of life. These strategies include octreotide therapy and continuous glucose monitoring.

Pancreatic insulinomas remain rare tumors, often discovered incidentally, making ongoing collection of epidemiological and pathological data essential for further improving their diagnosis and management.[59, 76–78]

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