HORMONES 2016, 15(4):489-499

Review

Glycemic control in patients with insulinoma

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ABSTRACT

Insulinoma is the most common neuroendocrine tumor of the pancreas. Surgical management of insulinomas is considered to be the only curative method. However, effective glycemic control preoperatively and in unresectable insulinomas remains a significant issue. Hyperinsulinism, occurring as a result of the hormone-secreting tumor, leads to life-threatening hypoglycemia episodes which require urgent medical treatment. This article discusses current management of hypoglycemia in insulinoma patients, including: education and lifestyle modifications, pharmacotherapy (diazoxide, somatostatin analogs, mTOR inhibitor – everolimus), cytoreductive methods and continuous glucose monitoring systems.

Key words: Insulinoma, Glycemic control, Hypoglycemia, Hyperinsulinism, Pharmacotherapy

INTRODUCTION

Insulinoma is a neuroendocrine tumor deriving from insulin-secreting pancreatic beta cells. Insulinoma is considered to be a rare type of tumor with an incidence estimated at 1 to 3 new cases per million persons per year occurring mostly between the ages of 41 and 50.[1] However, the incidence rate is likely to be underestimated due to the small size of the insulinomas. Most insulinomas are solitary, <2 cm in diameter and are equally distributed within the head, body and tail of the pancreas.[1,2] Only 3% of insulinomas are ectopic, of which the duodenal mucosa is the most common location. Multiple tumors are relatively rare and usually associated with the hereditary syndrome known as multiple endocrine neoplasia type 1 (MEN-1; 5-10%).[2] Benign insulinomas are found in approximately 90% cases, others exhibit malignant characteristics, i.e. local invasion into the surrounding soft tissue, lymph nodes or liver metastasis. Five-year survival has been reported to be at 97% for benign tumors and at 30% for malignant neoplasms.[3]

Clinical manifestations result from endogenous hyperinsulinism-related hypoglycemia identified when plasma concentrations of glucose are less than 55 mg/dl in non-diabetic individuals and no greater than 70 mg/dl in diabetic individuals.[4] Patients present with neuroglycopenic symptoms (confusion, disorientation, headache, behavioral and personality changes, visual disturbances, seizures and coma) and less often with autonomic symptoms caused by catecholamine response (diaphoresis, tremor, palpitations, weakness, hunger). Precipitating factors in the development of hypoglycemia include exercise or fasting. Pres-

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Received: 28-09-2016, Accepted 19-12-2016

ence of Whipple's triad (neuroglycopenic symptoms, low plasma glucose concentration, prompt relief of symptoms following the administration of glucose) is considered to be useful in establishing diagnosis; however, the 72-h monitored fasting test (together with measurement of the levels of plasma glucose, insulin, C-peptide and proinsulin) remains the gold standard for diagnosis of an insulin-secreting tumor. After biochemical confirmation of insulinoma, medical imaging is recommended.[2,5]

Surgical management giving the chance of full recovery remains the treatment of choice. Its efficacy in relieving the symptoms is estimated to be over 95%. During the perioperative period, in unresectable insulinomas or when surgery is contraindicated, adequate control of life-threatening hypoglycemia attacks is crucial.[5] The problem of refractory hypoglycemia especially affects patients with malignant insulinomas, as tumor progression makes the control of severe hypoglycemic episodes challenging. Risk of hormone-related death is serious, therefore symptoms control remains a priority.[6]

PREVENTION AND TREATMENT OF HYPOGLYCEMIA

Methods aimed at hypoglycemia prevention and treatment include patient education (also of their family and friends), lifestyle modification, pharmacotherapy, cytoreductive therapies and continuous glucose monitoring systems. They are summarized in Table 1.

General measures that patients suffering from hypoglycemia attacks should follow involve eating products rich in complex carbohydrates at regular intervals. Patients with glycemic fluctuations should avoid driving and excessive exercise. It is also recommended that education be provided to the patient's family and friends on recognizing and reacting to signs of hypoglycemia. In the event of manifestation of symptoms of hypoglycemia, immediate steps to restore normal blood glucose level should be undertaken. In conscious patients who are able to consume carbohydrates, 15 to 20 grams of glucose should be given every 15 minutes until the hypoglycemia has resolved. Carbohydrate-containing juice, soft drinks, milk, candy, other snacks or a meal can also be used. However, clinical improvement in insulin-induced hypoglycemia is usually transient and lasts less than 2 hours. Therefore, subsequent ingestion of meal rich in complex carbohydrates is advised. If the hypoglycemic episode is severe and the patient cannot ingest carbohydrates, parenteral glucose should be administered. Inpatients are given 25 gram boluses of 50% glucose until the hypoglycemia is managed. In order to sustain euglycemia in patients suffering from recurrent episodes of hypoglycemia, an infusion of 10% or 20% glucose may be used. Low blood glucose level in outpatients unable to ingest carbohydrates can be dealt with via intramuscular injection of 1 mg of glucagon.[4,7] Depending on the situation, enteral nocturnal feeding should be considered, and when severe hypoglycemia episodes occur – continuous glucose infusion with central venous catheterisation.[8]

As far as pharmacotherapy is concerned, proper treatment selection differs depending on whether the tumor is benign or malignant. These methods are discussed below.

DIAZOXIDE

Diazoxide, a benzothiadiazine derivative, is regarded as first-line treatment for glycemia control in insulinoma patients and is frequently used preoperatively when glucose administration fails to prevent hypoglycemia or to allow discharge home after surgery.[8-10] Diazoxide inhibits insulin secretion by opening ATP-dependent potassium channels in pancreatic beta cells.[1,8] In addition, the ability of diazoxide to increase hepatic glucose production and inhibit glucose uptake has been reported.[11]

The therapeutic daily dosage in adults is 3-8 mg/kg divided into two or three equal doses. In refractory hypoglycemia it may be higher.[12] Typical treatment should be initiated with a daily dose of 150 to 200 mg given in two or three doses per day. Then, depending upon the glucose level achieved, an appropriate dosage is applied up to a maximum of 600 to 800 mg per day.[13] A clinically relevant therapeutic effect should be achieved in several days. If it is not reached within 2-3 weeks, diazoxide treatment should be discontinued.[12] Diazoxide efficacy in decreasing frequency and severity of hypoglycemic attacks is estimated to be 50-60%.[14,15] Information on the ef-

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.	

fectiveness of treatment available from 39 questionnaires in a national UK survey showed that freedom from symptoms was achieved in 23 patients (59%). There was occasional hypoglycemia in 15 patients (38%). Frequent persistent symptoms during treatment occurred in only one patient.[15]

Approximately 50% of patients experience adverse effects during therapy.[14,15] The most common is edema due to water retention.[15] Fluid retention is dose-dependent and may appear after a few days of treatment.[10] Edema can be attenuated by thiazide diuretics as, apart from their diuretic action, a hyperglycemic effect of thiazide diuretics has been described.[1,8,15] Other frequent side effects include hirsutism, weight gain, nausea, emesis, diarrhea, abdominal pain, headache and rash.[14-16] In order to reduce nausea, patients are advised to take diazoxide with a meal.[13] Palpitation and renal malfunction have also been noted.[8,9] Any adverse effects that occur are generally not troublesome and the potential therapeutic benefits outweigh possible side effects.[14,15] In a national UK survey, side effects did not require interruption or modification of dosage.[15] Long-term treatment appears to be safe. In the aforementioned

UK survey, duration of treatment among 37 patients was 7 years (ranging from 1 to 22 years) and 11 patients (30%) had been taking diazoxide for over 10 years.[15] In another review patients had been treated with diazoxide for more than 20 years.[17]

Diazoxide is fetotoxic in animals and therefore contraindicated during pregnancy, unless the maternal hypoglycemia is life-threatening to the fetus. There is no evidence of transmission to breast milk.[10] It has been reported that somatostatin analogs may inhibit the hyperglycemic effect of diazoxide, thus simultaneous usage is not recommended.[8]

SOMATOSTATIN ANALOGS

Somatostatin analogs (octreotide, lanreotide) are considered second-line treatment for controlling the symptoms of hypoglycemia in patients with insulinomas. This method is used in patients with endogenous hyperinsulinism who are not eligible for surgery and when diazoxide is not applicable due to its inefficiency or adverse effects. Therefore, somatostatin analogs are not usually applied in benign cases where hypoglycemia can be successfully managed with meals and diazoxide before surgery.[8,14] Because of antiproliferative and moderate antineoplastic effect activity,[3,8] somatostatin analogs may be considered first-line treatment in malignant insulinomas.[8] Somatostatin is a peptide hormone which inhibits the motility and secretion of hormones (insulin, glucagon, secretin, VIP) in the digestive tract. In clinical practice, somatostatin analogs, octreotide and lanreotide are used instead of somatostatin due to their action being stronger than somatostatin, their longer half-life, the possibility of subcutaneous and intramuscular administration and absence of rebound hypersecretion.[18]

Somatostatin and its analogs exert their hypoglycemic effects by activation of somatostatin receptors (SST), leading to suppression of the insulin secretion. Analogs have a strong affinity for SST2 and SST5 and a lower affinity for SST3 receptors.[18,19] The hyperglycemic effect of somatostatin and its analogs results mainly from activation of the SST2 receptors, therefore it can occur only in insulinoma tumors in which they are expressed.[8] However, if the islets have a low expression of SST2, SST3 and SST5 receptors (or do not express them at all), somatostatin analogs can paradoxically lead to lower blood glucose by inhibition of glucagon secretion.[1,8]

Selection of patients who may benefit from somatostatin analogs administration should be based on positive somatostatin receptor scintigraphy known as OctreoScan.[19] This method includes intravenous administration of octreotide containing pentetreotide labeled with radioactive indium (^{111}In). In order to improve the detection rate of lesions, it is advisable to use single photon emission computed tomography (SPECT) concomitantly.[20] It should be pointed out that OctreoScan visualizes insulinomas that bear SST2 or SST5 receptors.[19] Therefore, malignant insulinomas, which often express these receptors, show positive somatostatin receptor scintigraphy in 73% of cases, while benign tumors are imaged in only 20-50% of patients.[21,22]

The most frequently observed adverse effects during therapy with somatostatin analogs include nausea, abdominal discomfort, diarrhea, flatulence and steatorrhea.[18,19] These effects appear within a few hours after the first injection of the drug, while their intensity is dose-dependent and usually disappears within the first 10-14 days of therapy.[18] It was also demonstrated that long-term (>1 month) treatment with somatostatin analogs is associated with an increased risk of gall stones or gallbladder sludge (20-50% of patients).[18,19]

In order to eliminate the abovementioned paradoxical hypoglycemia and to assess the tolerability of adverse effects from the gastrointestinal tract, treatment should be initiated via administration of the subcutaneous form of a short-acting drug combined with an observation stay of the patient in hospital.[1,3,8] Administration of 100-600 μg short-acting octreotide per day subcutaneously for the first 2 weeks is recommended. Subsequently, short-acting octreotide should be continued for another 2 weeks after the first dose of long-acting therapeutics is given (starting with 100-200 μg and increasing to the appropriate dose).[23] After achieving the desired response to the initial application of long-acting somatostatin analog, treatment is continued every two weeks (lanreotide 30 mg i.m.) or every month (20-30 mg i.m. octreotide and lanreotide 60-120 mg s.c.). The therapeutic effect is achieved after two weeks. Short-acting subcuta-

neously administered therapeutics can also be used in the course of long-term treatment as "rescue" injections in the case of exacerbated hypoglycemic symptoms.[19] In elderly patients and patients with renal impairment, prolongation of elimination half-life of the drug is observed, therefore dose adjustments may be necessary.[24]

It is estimated that long-acting therapeutics are effective in controlling the hypoglycemic symptoms in 35-50% of patients.[5] Long-term use of somatostatin analogs is limited by the development of tachyphylaxis.[25] After a few weeks or months of treatment, insulin secretion increases and symptoms of hypoglycemia worsen. Initially, the therapeutic effect can be maintained by increasing the dose, but eventually octreotide and lanreotide lose their effectiveness in all patients. Tumor cell loss of sensitivity to somatostatin analogs may be related to the growth of cancer cell clones not expressing the SST receptors.[18] In the absence of efficacy, somatostatin analogs should be discontinued because no benefits of combining these drugs with diazoxide have been observed.[8]

In cases of hypoglycemia not responding to octreotide or lanreotide, use of the second generation somatostatin analog pasireotide may be considered, as it has been reported to be more effective.[26] Although it is not registered for use in pancreatic NET, it displays a high affinity for SSTR1, SSTR2, SSTR3 and most importantly SSTR5 (up to 30-40% better compared with octreotide), which in particular is expressed in malignant insulinomas.[27,28]

EVEROLIMUS

Everolimus is the newest drug approved, in 2011, both by the US Food and Drug Administration and European Medicines Agency, for the treatment of well-differentiated and moderately differentiated non-operable pancreatic neuroendocrine tumors (NET) or metastatic pancreatic NET. Everolimus belongs to the group of mTOR inhibitors. mTOR inhibitors are drugs blocking the intracellular protein kinase mTOR, which is a component of signaling pathways regulating cell survival and growth, as well as angiogenesis.[29] Because of mTOR inhibitors' basic function, they are used as immunosuppressive agents in patients after transplantation and, due to their anti-proliferative activity, in invasive cardiology in coronary stents and in oncology as anticancer agents, including treatment of NET.[30]

In two randomized clinical studies everolimus was shown to be effective in the treatment of advanced pancreatic NET. In phase II of the RADIANT study, after 3 months, 77% of patients receiving everolimus displayed improvement or stabilization of disease.[31] In phase III of the RADIANT study, patients receiving everolimus demonstrated a reduction in tumor progression (assessed radiographically) by as much as 65% compared to the placebo group and reduction in tumor size in 64% of patients in the treatment group.[29] One of the most common adverse effects observed (in about 13% of patients) was hyperglycemia. The observed hyperglycemia, which in other applications was an adverse effect, became the basis for attempts to use this drug for controlling symptoms of insulinoma. Though the RADIANT studies included mostly non-functional pancreatic NET and there were only a few cases of insulinoma, the French group retrospectively analyzed insulinoma cases and noted the added benefit of improved glycemic control in 11 out of the12 patients treated with everolimus.[32] There have been no other clinical studies but the effectiveness of everolimus in preventing hypoglycemia in patients with insulinoma was confirmed in many case reports.[33-41] They are summarized in Table 2.

The efficiency of everolimus in normalization of glucose levels may be explained only partially by its effect on tumor regression, as it was also observed in patients with no evidence of an antitumor effect of the drug.[32-36,39] Several possible mechanisms of everolimus hyperglycemic activity have been proposed. Everolimus may reduce production and secretion of insulin[33] due to mTOR inhibition downstream of insulin receptors[36] as well as through mTORC2 and alteration of Akt signaling.[42] Everolimus also increases peripheral insulin resistance by downregulation of glucose transporter 1 (GLUT1) by reduced transcription and translation of GLUT1 to the plasma membrane due to Akt-inhibition as a result of reduced mTORC2 formation.[33] Moreover, an increase of hepatic gluconeogenesis by everolimus is possible due to inducing transcriptional activation of gluconeogenic genes via the coordinated activation of PGC-1, CRTC2, CREB and FoxO1.[43]

Table 2. Case reports of everolimus treatment in patients with insulinoma. M - male, F - female, mo - months.

Study	Age, sex	Previous hyperglycemic treatment	Glycemic effect	Tumor response
Kulke et al (2009)[36]	57, F	Octreotide, diazoxide, dexamethasone, frequent meals, nocturnal infusions	Normalization of glucose level; discontinuation of diazoxide and nocturnal infusions	Partial response for 16 mo
	40, F	Octreotide, diazoxide, glucose tablets	Normalization of glucose level; discontinuation of diazoxide and glucose tablets	Partial response for 29 mo
	22, F	Octreotide, diazoxide	Normalization of glucose level; discontinuation of diazoxide	Stable disease for >6 mo
	66, M	Nocturnal dextrose infusion	Normalization of glucose level; discontinuation of nocturnal dextrose infusions	Stable disease for >6 mo
Ong et al (2010)[37]	64, M	Diazoxide, prednisolone. octreotide, continuous dextrose infusion	Normalization of glucose level; discontinuation of diazoxide, prednisone, octreotide and continuous dextrose infusion	Partial response for 7 mo
Fiebrich et al (2011)[33]	60, M	Frequent meals, octreotide, glucose infusions	Normalization of glucose level; discontinuation of glucose infusions	Partial response for 8 mo
	75, F	Frequent meals, octreotide	Normalization of glucose level	Partial response for 8 mo
	55, M	Frequent meals, octreotide, glucose infusions	Normalization of glucose level; discontinuation of glucose infusions	Stable disease for 5 mo
Ferrer-García et al (2011)[39]	78, M	Diazoxide, dexamethasone, octreotide	Normalization of glucose level; discontinuation of dexamethasone	Stable disease for 6 mo
Bozkirli et al (2013)[38]	61, F	Octreotide, continuous dextrose infusion	Normalization of glucose level, discontinuation of continuous dextrose infusion and octerotide	Partial response for 2 mo
Asayama et al (2014)[34]	57, F	Octreotide, diazoxide, nocturnal glucose infusion	Normalization of glucose level; discontinuation of glucose infusion, diazoxide and octerotide	Stable disease for >12 mo
Baratelli et al (2014)[35]	60, M	Glucose infusions, prednisone, diazoxide, octreotide, recombinant glucagon on demand, frequent meals, nocturnal infusions	Normalization of glucose level; discontinuation of glucose infusions, prednisone, diazoxide, recombinant glucagon	Stable disease for 16 mo
Nahmias et al (2015)[40]	45, F	No previous treatment	Normalization of glucose level	Partial response for 18 mo
	63, M	No previous treatment	Normalization of glucose level	No information
	66, M	No previous treatment	No effect	No information
Dubey and Viswanath (2016)[41]	58, F	Dextrose infusions, octreotide	Normalization of glucose level; discontinuation of dextrose infusions	No information

Everolimus is administered at a dose of 10 mg per day in patients with insulinoma.[29] A clinical effect may be achieved quickly, within 2 weeks of everolimus treatment.[33,34,37,38,41] After some time of treatment everolimus may lose its therapeutic effect, but the efficiency loss is probably only transitory: in one study, after discontinuation of the everolimus therapy and re-administration of the drug, an improvement in glycemic control was observed.[35] Everolimus adverse effects include stomatitis, mouth ulcers, rash, diarrhea, fatigue, infections (mostly upper respiratory tract) and complete blood count abnormalities in the form of mild neutropenia and anemia.[29] In the case of serious adverse events, reduction of the dose to 5 mg/day may be considered, as everolimus also shows clinical effectiveness at lower doses; in some cases no recurrence of hypoglycemia was observed after dose reduction.[32,34,37,39]

OTHER PHARMACOLOGICAL METHODS

Drugs known to have hyperglycemic adverse effects were used before the introduction of newer pharmacological methods for the treatment of hypoglycemia in insulinoma patients. For instance, treatments with glucocorticoids, beta blockers, calcium channel blockers and phenytoin were attempted, though none of them were routinely applied in insulinoma patients.

Glucocorticoids are known to participate in the regulation of carbohydrate balance. They raise the blood glucose level by increasing insulin resistance, stimulating gluconeogenesis, decreasing glucose uptake and inhibiting synthesis of insulin. The most frequently used drug of this group in patients with insulinoma was prednisone.[44-46] However, glucocorticoids have never attained a broader application in the treatment of hypoglycemia due to its wide range of adverse effects (including hypertension, osteoporosis, edema, increased susceptibility to infections). Today, the simultaneous use of glucocorticoids and everolimus is contraindicated.

The hyperglycemic effect of beta blockers, which are frequently used cardiac drugs, has not been fully explained. Beta blockers decrease insulin sensitivity probably due to their impact on pancreatic beta cells and on peripheral insulin sensitivity. Most treatment approaches in insulinoma patients were made using propranolol at a dose of up to 240 mg.[47-49] Although beta blockers are usually well tolerated (the most common adverse effects include bradycardia, atrioventricular conduction disturbances, hypotonia), they never demonstrated sufficient hyperglycemic efficacy.

Phenytoin, mostly used as an anticonvulsant, can decrease insulin secretion by sodium channels inhibition, decrease of calcium ions influx and calcium-calmoduline complex inhibition. Therefore, phenytoin (at a dose of 300-800 mg per day) was attempted in several cases to treat hypoglycemia in patients with insulinoma.[50-52] With reported mixed effectiveness and a large number of adverse effects (including neurological disorders such as nystagmus, somnolence, impaired speech and motor coordination, ataxia or polyneuropathy), phenytoin never found clinical application in insulinomas.

Calcium channel blockers (CCBs), a group of drugs commonly used in cardiology, are able to decrease insulin secretion (despite the fact that in long-term usage they do not affect the carbohydrate balance of patients). Application of this feature was attempted in the treatment of hypoglycemia in patients with insulinoma by administration of verapamil at a dose of 80 mg per day.[53-55] The efficacy of CCBs in treating hypoglycemia is questionable.

The clinical usefulness of the aforementioned drugs in the treatment of hypoglycemia in patients with insulinoma is doubtful because of the negative efficiency to adverse effects ratio. Their application may be carefully considered in rare cases of inefficiency of standard pharmacotherapy or in insulinoma patients with comorbidities requiring their usage.

CONTINUOUS GLUCOSE MONITORING SYSTEMS

Continuous glucose monitoring systems (CGMS) may be considered useful in the treatment of challenging hypoglycemic episodes, e.g. in patients with unawareness of hypoglycemic episodes or in cases of problems in maintaining blood glucose. In CGMS, the glucose level is monitored indirectly by measuring the level of hydrogen peroxide that is formed by the reaction between glucose, oxygen and water catalized by the glucose oxydase enzyme.[56] The most advanced

systems are connected to an infusion pump automatically administering, depending on the need, the right amount of insulin or glucose.[3] The usefulness of CGMS in enabling detection of hypoglycemia episodes and in monitoring the effectiveness of applied treatment was reported in a few cases.[57-60] Unfortunately, CGMS clinical use is limited due to its high cost and low availability and the several technical issues they still exhibit (requirement of frequent calibration and not always accurate measurement of glucose levels).[56]

SURGICAL AND CYTOREDUCTIVE METHODS

The management of malignant insulinomas is a serious challenge for clinicians and the use solely of pharmacotherapy may not be sufficient. In order to improve glycemic control, a decrease in hormonal secretion can be achieved by applying invasive methods, i.e. debulking surgery and liver metastases cytoreductive therapy (TAE, TACE, SIRT). Chemotherapy and peptide receptor radionuclide therapy (PRRT) are also considered important therapeutic options.[6,61]

Cytoreductive surgery in advanced malignant insulinoma contributes to improved glycemic control and renders systemic therapy more effective. Therefore, palliative surgery to remove or debulk the primary tumor is recommended. However, there are some restrictions involved: location and extension into surrounding tissues must be evaluated accurately, the mesenteric artery cannot be invaded and at least 90% resection of the tumor is required to achieve a decrease in hormonal hypersecretion.[8,62] In certain cases of severe hypoglycemia, less extensive surgery is performed, resecting 60-70% of liver metastases. The benefits, however, remain undetermined.[8]

If liver tumor bulk cannot be dealt with via surgery, there are minimally invasive locoregional approaches to be considered. Liver metastases cytoreductive therapy options include trans-arterial embolization (TAE), trans-arterial chemoembolization (TACE) and selective internal radiation therapy (SIRT).[63] As far as TAE and TACE are concerned, tumor response rates in pNETs range from 35% to 80%. Symptomatic response is reported to be 70-100% with a median progression-free survival rate of 10-30 months and overall survival of 20-36 months.[64] SIRT studies revealed 1-year stable disease in 60-67% and primary relief in symptoms in approximately 80% of patients.[65]

Peptide receptor radionuclide therapy applies somatostatin analogs coupled with β-emitting radionuclides yttrium (^{90}Y) and lutetium (^{177}Lu). Subsequently, they are internalized within neuroendocrine cells after their binding to the SSTR.[8] PRRT has been described as a valuable method in the case of refractory hypoglycemia due to malignant insulinoma.[6,8,66] However, this option requires more investigation, as serious side effects are observed.[66]

Chemotherapy has been described as an important method to be applied in pNETs. Administration of streptozocine combined with 5-fluorouracil (FU) and/or doxorubicin resulted in objective response in 6-70% of patients with pNETs. However, these surveys are limited, as the evaluation of the effects of chemotherapy on patients with all types of pNETs were investigated, while precise data on insulinomas are lacking.[6]

CONCLUSION

Insulinoma, as a hormonally active tumor, can cause diagnostic and therapeutic difficulties for physicians. Due to life-threatening hypoglycemia episodes, one of the biggest challenges in treating patients with insulinoma is maintaining the correct glucose blood levels. Fortunately, in recent years expansion of therapeutic possibilities to control glycemia have been achieved. These possibilities include education and lifestyle modification of patients, pharmacotherapy, cytoreductive methods and the use of continuous glucose monitoring systems. In this study we have described a wide range of therapeutic methods, thereby proposing strategies to apply the most individualized and effective procedures for the patient, which increase the potential to extend and improve the quality of life of patients with insulinoma.

FOUNDING

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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