

The treatment of hyperinsulinemic hypoglycaemia in adults: an update

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Abstract

Background Treatment of hyperinsulinemic hypoglycaemia (HH) is challenging due to the rarity of this condition and the difficulty of differential diagnosis. The aim of this article is to give an overview of the recent literature on the management of adult HH.

Methods A search for reviews, original articles, original case reports between 1995 and 2016 in PubMed using the following keywords: hyperinsulinemic hypoglycaemia, insulinoma, nesidioblastosis, gastric bypass, autoimmune hypoglycaemia, hyperinsulinism, treatment was performed.

Results One hundred and forty articles were selected and analysed focusing on the most recent treatments of HH.

Conclusions New approaches to treatment of HH are available including mini-invasive surgical techniques and alternative local–regional ablative therapy for benign insulinoma and everolimus for malignant insulinoma. A

correct differential diagnosis is of paramount importance to avoid unnecessary surgical operations and to implement the appropriate treatment mainly in the uncommon forms of HH, such as nesidioblastosis and autoimmune hypoglycaemia.

Keywords Hyperinsulinemic hypoglycaemia · Treatment · Insulinoma · Nesidioblastosis · Autoimmune hypoglycaemia

Abbreviations

HH	Hyperinsulinemic hypoglycaemia
pNET	Pancreatic neuroendocrine tumour
SSTR	Somatostatin receptors
INF- α	Interferon- α
TAE	Trans-arterial embolization
TACE	Trans-arterial chemoembolization
SIRT	Selective internal radiation therapy
PRRT	Peptide receptor radionuclide therapy
NIPHS	Noninsulinoma pancreatogenous hypoglycaemia syndrome
RYGB	Roux-en-Y gastric bypass

Classification and diagnostic overview

The hyperinsulinemic hypoglycaemia (HH) is a rare condition characterized by inappropriate insulin secretion in the presence of hypoglycaemia. It should be suspected in the presence of Whipple's triad: symptoms or signs consistent with hypoglycaemia, low plasma glucose level and relief of symptoms after administration of glucose. Symptoms of hypoglycaemia are classified as neuroglycopenic due to brain glucose deprivation and autonomic due to adrenergic activation. The first group ranges from dizziness, mental

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confusion, abnormal behaviour to epilepsy and coma; the second group comprises adrenergic symptoms such as palpitations, tremor, anxiety and cholinergic symptoms such as sweating, hunger and paresthesias [1, 2]. In 2009, the Endocrine Society's guidelines for evaluation and management of hypoglycaemic disorders established a new classification, no longer based on the timing of the hypoglycaemic symptoms, i.e. fasting versus postprandial, but on the patients' health status [3]. Consequently, HH should be suspected in an apparently healthy patient after exclusion of drug assumption, hormonal deficiency, critical illness or nonislet cell tumours. The most common cause of HH in adults is the insulinoma, a generally benign pancreatic neuroendocrine tumour (pNET) with an incidence of 4 cases per million per year [4–6]. The noninsulinoma pancreatogenous hypoglycaemia due to beta-cell hyperplasia is another even rarer cause, accounting for 4 % of all cases of HH [7]. Recently, it has been increasingly reported in patients who have undergone a gastric bypass for severe obesity. Furthermore, autoimmune hypoglycaemia due to insulin antibodies or insulin receptor antibodies must be taken into account in the differential diagnosis of HH to avoid misleading diagnosis of insulinoma. Treatment of HH is challenging due to the rarity of this condition and the difficulty of a correct diagnosis, mainly that of the less frequent form of HH. The aim of this review is to give an overview of the recent literature on the management of HH.

Treatment of benign insulinoma

Surgery

The surgical resection of insulinoma represents the treatment of choice since most tumours are small (<2 cm) and benign [8, 9]. The tumour enucleation, using an open or laparoscopy approach, is the advisable option whenever possible [10–18]. The successful surgical rate ranges from 75 to 98 %. Given the multiplicity and the risk of malignancy of insulinomas in MEN1 patients, the choice of which surgical approach to perform is debatable. Pancreatic resections are suggested by several authors in order to provide long-term cure [13, 19, 20]. However, due to lower morbidity enucleation of all insulinomas might be considered as an alternative to distal or total pancreatectomy [10, 21, 22]. The relapse rate of insulinoma after surgery is low (3–7 %) in sporadic cases compared to MEN1 patients (21 %) after a 20-year follow-up [12–23]. In the last few years, robotic-assisted techniques have become feasible also for the resection of small pNETs, including insulinoma [10, 11]. However, the surgical indications and results are still ongoing [24].

Local–regional ablative therapy

In patients at high surgical risk or in those refusing surgery, alternative local regional therapies can be offered. Several case reports and small series have been published reporting successful treatment of hypoglycaemia by transcutaneous or laparoscopically radiofrequency ablation, high-intensity focused ultrasound ablation (HIFU), ultrasound-assisted alcoholization or selective chemoembolization [25–32]. However, follow-up of patients treated with locoregional therapies is generally short, ranging from 5 weeks to 9 months; thus, additional data are needed to validate these techniques.

Hypoglycaemia symptomatic therapy

During the pre-operative phase, 10 % glucose solution is usually administered and continued for an additional 24-h period after surgery. Serum glucose levels typically rise 1 h after the successful removal of the insulinoma, but in 20 % of cases the glucose increase can be delayed [5].

Patients waiting for the operation, or who are not candidates for or refuse surgery, or in whom surgical treatment has not been successful, can be treated medically to control the hypoglycaemic episodes [33]. Besides pharmacological treatment, patients should follow a fractioned diet including complex carbohydrates with slow absorption and simplex carbohydrate with fast absorption in case of hypoglycaemic crisis. Diazoxide, the most used drug, inhibits insulin release by opening the ATP-dependent potassium channel in pancreatic β cells. It is effective in controlling the hypoglycaemic episodes in more than half of the patients in fractioned doses ranging from 100 to 600 mg up to 1500 mg per day [34]. Because of the sodium retention side effect, it is often given in association with a thiazidic diuretic. Moreover, it can provoke gastrointestinal side effects such as nausea and vomiting and hirsutism [35].

Given the inhibitory effect of insulin secretion by somatostatin analogues and the presence of somatostatin receptors (SSTR)2A-SSTR5 in a subgroup of insulinomas, octreotide has been demonstrated as an effective treatment of hypoglycaemia in about 50 % of patients. A positive short test with subcutaneous octreotide is predictive of the efficacy of the treatment, while a positive result of Octreoscan scintigraphy is not predictive [36, 37]. Moreover, the test is useful to predict a paradoxical worsening of hypoglycaemia that can occur due to the suppression of the counter-regulatory hormones glucagon and growth hormone, mainly during treatment with long-acting somatostatin analogues [38, 39]. In the case of a malignant insulinomas, somatostatin analogues have been reported as less effective [35].

SSTR subtype expression differs between benign and malignant insulinomas, even though there are conflicting data [40]. Bertherat et al. [41] found that SSTR2 and SSTR5 are the most frequently expressed SSTRs in insulinomas. In most of the tumours they investigated, that were mainly benign, higher expression of SSTR2 than of SSTR5 was observed, but a subgroup of tumours presented higher expression of SSTR5 than of SSTR2. Portela-Gomes et al. [42] found that SSTR4 was the most frequently expressed SSTR in both benign and malignant insulinomas. The malignant tumours, but none of the benign tumours, also expressed SSTR5. In this series, all other receptor subtypes were expressed in low numbers, and no difference between benign and malignant insulinomas was found. In the study by de Sá et al. [40] SSTR5 mRNA was positively correlated with histopathological features related to tumour aggressiveness (large tumour diameter, well-differentiated endocrine tumour with uncertain behaviour and higher number of cells with nuclear atypia). Finally, in malignant insulinomas a higher expression of SSTR compared with benign insulinomas has been described [43].

Finally, in the case of refractory hypoglycaemia, treatment with glucocorticoids can be used because it induces hyperglycaemia by inhibiting insulin release and increasing peripheral insulin resistance [33].

Treatment of refractory hypoglycaemia in malignant insulinoma

Malignant insulinoma accounts for 10 % of all cases of insulinoma. It displays a poor prognosis and represents a double therapeutic challenge for clinicians: the control of tumour progression and the control of severe hypoglycaemic syndrome. The risk of hormone-related death or complications makes symptoms control of primary importance.

Recently, a better understanding of molecular pathways has provided clues for new therapeutic strategies and a variety of targeted agents have been explored in pNETs.

Hormonal syndrome control

Everolimus

Everolimus acts as inhibitor of mTOR signalling pathway, which plays a key role in the control of cell growth, proliferation as well as lipid and glucose metabolism [44, 45]. This oral anticancer drug has recently been shown to improve progression-free survival of patients with well-differentiated progressive metastatic pNET (RADIANT III study) [46] and has been approved by FDA in 2011 for this indication [47]. It may have synergistic antitumour effects when combined with somatostatin analogues [48]. In several studies

hyperglycaemia and diabetes have been recognized as a frequent adverse event of everolimus [46, 49, 50], making the drug appealing to the management of insulinoma.

Initial case reports and small series of patients with insulinoma and untreatable hypoglycaemia found that everolimus was able to induce a rapid normalization of blood glucose levels in a few days, allowing glucose infusion to discontinue in several cases or the withdrawal of all other treatments for several months [45, 51–54]. The French Group of Endocrine Tumors has recently shown that 11 out of 12 patients with metastatic insulinomas and refractory hypoglycaemia had a complete clinical response with everolimus treatment, although they previously experienced a median failure of four different treatment lines [55].

The exact mechanism by which everolimus can control hypoglycaemia in patients with insulinoma is not fully elucidated, and several mechanisms can be considered, including an increase in peripheral insulin resistance and a decrease in beta-cell proliferation, survival and metabolism [45, 49]. The effect of everolimus in insulinoma-induced hypoglycaemia has also been reported in patients who did not have tumour regression [51, 55, 56], suggesting that disease progression and/or increased levels of insulin may not be considered the only criteria for discontinuing everolimus therapy when hypoglycaemia is controlled [57].

Sunitinib

Sunitinib, a multiple tyrosine kinase inhibitor that target vascular endothelial growth factor receptor and platelet-derived growth factor receptor [56, 58], is another oral anticancer agent approved in the treatment of progressive advanced pNET [59]. Unlike everolimus this drug does not have direct effects on glycaemic control. Some studies even reported the risk of onset of severe hypoglycaemia with sunitinib [60, 61], making its use in the treatment of malignant insulinoma still questionable [62, 63].

Interferon- α

Interferon- α (IFN- α) is a biological agent with direct action on cell cycling, angiogenesis and modulation of immune response. The drug has antisecretory and antiproliferative efficacy in NET, similar to those of somatostatin analogues [64]. However, INF- α does not act as rapidly as somatostatin analogues and has a less favourable safety profile, with commonly reported adverse events such as fever, fatigue, anorexia and weight loss [58]. Due to toxicity profile, the drug mainly is a role as a second-line option in the refractory setting [64, 65]. INF- α is not generally recommend in the treatment of insulinoma. Indeed, the use of INF- α in the treatment of malignant insulinoma was reported only in the past, as anecdotal experiences [66], without proof of real efficacy.

Pasireotide

Pasireotide (SOM230) is a new multi-receptor-targeted somatostatin analogue. As compared with octreotide, pasireotide exhibits a binding affinity 30–40 times higher for human SSTR1 and SSTR5 and 2.5 lower for human SSTR2. Owing to the promising results obtained in the treatment of patients with acromegaly and Cushing's syndrome, investigation on NETs was initiated. The most frequent adverse events reported were nausea, abdominal pain and hyperglycaemia. In particular, a recent phase II trial with pasireotide long acting conducted in grade 1 or 2 NETs reported a 79 % rate of hyperglycaemia, including 14 % of grade 3 hyperglycaemia [67]. The hyperglycaemic effect of pasireotide, greater than other somatostatin analogues (octreotide, lanreotide), can be explained by the different binding affinities of pasireotide to SSTRs and by the subtype-selective expression of SSTRs in pancreatic islet cells. Immunocytochemistry study showed that SSTR1 and SSTR5 were co-localized with insulin in almost all β cells, whereas SSTR2 was found in only 46 % of β cells. Conversely, SSTR2 was co-localized with glucagon in most of α cells [68]. Thus, pasireotide, with a high binding affinity to SSTR1 and SSTR5, exhibits a strong inhibitory effect of insulin secretion with no significant effect on glucagon release.

Currently, pasireotide is still not registered for the treatment of NET and we are waiting for the results of ongoing trials.

Given that SSTR1 and SSTR5 may have an inhibitory effect on cell proliferation and that SSTR5 is involved in insulin secretion control [69], SOM230 would have the potential to promote size reduction and inhibition of insulin secretion in insulinomas [40].

Studies on pNET in mouse model have indeed shown the antisecretory, antiproliferative and proapoptotic activity of the drug in MEN1 model of insulinoma [70, 71]. Moreover, a paper was recently published reporting the efficacy of pasireotide in treatment of refractory hypoglycaemia due to malignant insulinoma [72].

On the basis of these preliminary data, pasireotide could be considered a novel therapeutic option for symptom control in malignant insulinoma. However, further studies on its effects in refractory hypoglycaemia are warranted.

Antineoplastic treatment

Chemotherapy

Chemotherapy has a critical role in the management of metastatic and progressive insulinomas. A variety of systemic chemotherapy regimens have been explored in patients with pNETs, including insulinomas. streptozotocin

combined with 5-fluorouracil (FU) and/or doxorubicin has been used, resulting in objective response (OR) in 6–70 % of patients with pNETs [73–77]. The combination of capecitabine and temozolomide has also been evaluated, and OR of 70 %, a median progression-free survival (PFS) of 18 months and 2-year survival of 92 % have been reported [78]. Favourable results have also been obtained, testing dacarbazine as a second-line therapy. Dacarbazine alone achieved an OR of 34 % [79], while in combination with 5-FU and epirubicin, the OR was 20–40 % and the PFS 11–21 months [80]. In addition, recent studies evaluated the use of combined gemcitabine and oxaliplatin as first-line treatment in 37 patients with pNETs, resulting in OR in 38 % of patients and PFS of 7.3 months [81]. However, the above-mentioned studies are limited regarding the evaluation of the effects of chemotherapy on patients with all types of pNETs, while specific data on insulinomas are lacking. Generally, nonfunctioning pNETs are overrepresented in these studies, while malignant insulinomas are rare and not even included in the studies.

Debulking surgery

Cytoreductive surgery, when feasible, may decrease the hormonal secretion and also makes systemic therapy more effective. Thus, in advanced malignant insulinoma palliative surgery to remove or debulk the primary tumour is recommended, but depends on its location and extension into surrounding tissues [58]. Mesenteric artery invasion is a contraindication to surgery [62], and at least 90 % resection of the tumour is typically required to achieve symptom control [58]. Improved outcome has been demonstrated in patients with islet cell cancer and synchronous hepatic metastases managed aggressively with debulking surgery [82, 83].

Surgery of liver metastases is of interest when more than 90–95 % of the macroscopic tumour mass can be removed and/or hypoglycaemic syndrome is refractory. In certain cases of severe hypoglycaemia, less ambitious surgery is undertaken, resecting 60–70 % of the liver metastases. The benefit however remains undetermined [62].

Liver metastases cytoreductive therapy (HAE/TACE, SIRT)

Metastatic involvement of the liver typically develops in about 46–93 % of NETs [84]. P-NETs show liver metastases either at initial evaluation or during the course of their disease in 30–85 %. About 10 % of insulinoma present liver metastases [85]. Presence and extension of liver metastases are considered important prognostic factors for NETs as they may significantly impair the patient's quality of life either because of tumour bulk or hormonal hypersecretion [86]. Liver metastases can result in a gradual

replacement of liver parenchyma resulting in a progressive deficit of function until death, thus decreasing long-term survival. Treatment of liver metastases can be curative or palliative. An effective treatment has to result in control of tumour growth and systemic hormonal effect, improvement of quality of life. In most NETs patients with liver metastases, minimally invasive, locoregional approaches are adopted in place of surgery which remains the first option if possible. They include trans-arterial embolization (TAE), trans-arterial chemoembolization (TACE), selective internal radiation therapy (SIRT) [87].

TAE is based on selective infusion of particles in the branch (segmental or subsegmental) of the hepatic artery supplying the tumour lesions. The goal of TAE is to occlude tumour blood vessels resulting in ischaemia and necrosis. TACE differs from TAE for the administration of a chemotherapeutic agent (anthracyclines such as doxorubicin or epirubicin) mixed with lipiodol (fat-soluble contrast medium with high concentration of iodine), into the hepatic artery followed by the administration of embolizing agents. In TAE treatment, lipiodol administration (50 %) is followed by the administration of embolizing agents [88].

Indications for TAE/TACE generally include unresectability with symptoms related to tumour bulk, excessive hormone production and rapid progression of liver disease. Many reviews have been published on locoregional ablative treatments of liver metastases of all NETs and reported that TAE and TACE appear to be an optimal treatment approach for inoperable liver metastases from NETs for palliation of hormonal symptoms and pain, improvement of biomarkers and reduction of tumour burden [87–89]. A growing interest in local treatment options lies in the use of SIRT using yttrium-90 (^{90}Y). ^{90}Y is high-energy β -emitter with a mean tissue penetrance of 2.5 mm. This is attached to microspheres measuring 20–40 μm in size. Due to the local application, a radiation dose of up to 1000 Gy can be administered to the tumour, causing local destruction. As this is a relatively new method, only a few studies exist, showing a 1-year stable disease in 60–67 % and a primary relief in symptoms in roughly 80 % of patients. In those studies, especially patients with large volume tumours were included [90]. However, to clarify the value of these regimens in the treatment of hepatic metastases, further investigation is warranted.

Regarding insulinoma, liver metastases are the major cause of post-operatively persistent hypoglycaemia, although due to the small number of metastatic insulinomas, no controlled studies of the therapeutic effect of the above-mentioned interventions exist for this specific kind of tumour. Infrequent case reports that include one or several patients and feature unusual aspects of the disease are available. Affected patients are usually included with other NET patients in study protocols intended to evaluate the effectiveness of chemotherapy or adjuvant treatments

such as somatostatin analogues [91, 92]. Satrke et al. [93] reported on 10 patients with metastatic malignant insulinoma, treated with repeated TACE and chemoperfusion protocols using high-dose transhepatic streptozotocin perfusions (3–4 g per session). The current median survival time for all 10 patients is 2.6 years (range 1.6–9.7 years). Six patients are currently alive with a median survival of 3.7 years (1.7–9.7 years), five of them with stable disease and free of hypoglycaemia. Four patients died after a median survival of 1.8 years (range 1.6–7.5 years) from complications of unmanageable hypoglycaemia.

Peptide receptor radionuclide therapy (PRRT)

PRRT uses somatostatin analogues coupled with β -emitting radionuclides yttrium (^{90}Y) and lutetium (^{177}Lu), which internalized within neuroendocrine cells after their binding to the SSTR [62]. Yttrium and lutetium differ from one another in terms of emitted particles, particle energy and tissue penetration.

As a prerequisite for this therapy, the presence of SSTR subtypes on tumour cells has to be demonstrated. For this purpose, in vivo ^{111}In -pentetreotide scintigraphy, or ^{68}Ga -DOTANOC PET, and SSTR immunohistochemistry on tumour specimens have been used [56]. To maximize the effect of therapy, treatment with short-acting somatostatin analogues has to be discontinued 1 day before PRRT and 6 weeks by the treatment with long-acting somatostatin analogues. PRRT is arising as effective treatment in GEP-NETs with promising results in nonrandomized trials, including pNET [94, 95]. Symptomatic responses to PRRT have been observed in case of malignant insulinoma with refractory hypoglycaemia [52, 96, 97], also when objective measurable tumour response was minimal or absent [56]. The main long-term side effects reported were loss of renal function, pancytopenia and myelodysplastic syndrome. Age exceeding 70 years, bone metastasis, previous chemotherapy and creatinine clearance less than 60 ml/min are predictive factors for higher toxicity [62].

PRRT can be considered as an important therapeutic option in case of refractory hypoglycaemia due to malignant insulinoma, although currently the treatment is still deemed as investigational and its implementation must comply with national legislation and ethical guidelines [98].

Treatment of noninsulinoma pancreatogenous hypoglycaemia

Nesidioblastosis

In 1938, Laidlaw described nesidioblastosis as a functional disorder of non-neoplastic beta cells [99] characterized by

Table 1 Causes of hypoglycaemia in adults*Ill or medicated individual*

1. Drug or alcohol assumptions (insulin or other insulin secretagogues)
2. Critical illnesses: hepatic, renal or cardiac failure, sepsis
3. Hormone deficiency: cortisol, glucagon and epinephrine in type 1 diabetes mellitus
4. Nonislet cell tumours

Apparently healthy individual (hyperinsulinemic hypoglycaemia)

1. Insulinoma
2. Noninsulinoma pancreatogenous hypoglycaemia:
 - a. Idiopathic nesidioblastosis
 - b. Upper gastrointestinal surgery hypoglycaemia
3. Autoimmune hypoglycaemia:
 - a. Anti-insulin antibodies (insulin autoimmune syndrome or Hirata syndrome)
 - b. Anti-insulin receptor antibodies (type B insulin resistance)

combined hyperplasia, diffuse proliferation and hypertrophy of islet cells from pancreatic ducts [100, 101]. This clinical entity, also referred as noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS), currently represents 0.5–5 % of organic hyperinsulinemia causes [102]. Diagnostic criteria for NIPHS include positive Whipple's triad, a negative 72-h fast, negative perioperative imaging studies for insulinoma, positive arterial calcium stimulation test [103] and islet hypertrophy or nesidioblastosis in pancreatic tissue [101]. NIPHS has been identified both in patients with idiopathic nesidioblastosis and in patients who had upper digestive bariatric surgery. Idiopathic nesidioblastosis is generally secondary to genetic abnormalities such as the mutations in SUR1 and Kir6.2 genes, which encode proteins involved in beta-cell function [104, 105]. However, these genetic abnormalities have not been described in adults [101, 106], even though other genetic mutations, as yet unspecified, might be supposed. Alternatively, it has been suggested that calcium ions may directly trigger the release of β -cell peptides from tumorous β cells by a, yet undefined, mechanism not shared by normal β cells [107]. Currently, subtotal esophagectomy, subtotal gastrectomy, roux-en-Y gastric bypass (RYGB), Billroth I partial gastrectomy and Billroth II gastric bypass surgeries have all been associated with NIPHS, while gastric banding procedures have been shown to induce transient asymptomatic HH [108–110]. The phenomenon of hypoglycaemia in post-RYGB patients is becoming increasingly common, and a prevalence of 0.36 % has estimated. At least 40 cases of nesidioblastosis have currently been reported after RYGB [108, 111]. However, the pathogenetic mechanisms of nesidioblastosis in post-RYGB patients are not fully understood. On the one hand, the change in gastrointestinal architecture might contribute to the pathogenesis of NIPHS [112]. On the other hand, the consequent weight loss and reduction of insulin resistance might unmask a primary underlying condition [113, 114]. In this view are the

findings that some patients with RYGB history did not have histologic criteria for nesidioblastosis [115], suggesting that some patients might have a pre-nesidioblastosis lesion prior to their surgery, due to genetic or obesity-related effects [116]. Therefore, potential mechanisms of acquired nesidioblastosis after gastric bypass include obesity-induced adaptive beta-cell hypertrophy, increased growth factors release and altered gut hormonal signalling [108, 111, 115–119]. Glucagon-like peptide-1 (GLP-1) might play a crucial role, inducing the expression of the transcription factor pancreatic-duodenum homeobox-1 (PDX-1) that regulates islet growth [120]. Further, other factors such as IGF-2, IGF-1 alpha receptor, TGF beta receptor and ghrelin might be involved in nesidioblastosis pathogenesis [118]. Medical treatment, consisting of low-carbohydrate diet in combination with compounds such as diazoxide, octreotide, acarbose or calcium channel blockers (such as verapamil and nifedipine), should be first started [121–124]. However, distal, subtotal and near-total pancreatectomy in severe cases of nesidioblastosis and in patients with history of upper gastrointestinal surgery might be required [110, 117, 125] (Tables 1, 2).

Autoimmune hypoglycaemia

Autoimmune hypoglycaemia is characterized by elevated levels of insulin, hypoglycaemia and anti-insulin antibodies (insulin autoimmune syndrome, Hirata syndrome) or anti-insulin receptor antibodies (type B insulin resistance). In these syndromes are present postprandial hypoglycaemia, fasting hypoglycaemia or both [126].

Hirata syndrome is a rare condition in Western countries, whereas in Japan it is the third cause of hypoglycaemia [127]. Episodes of HH mainly in the postprandial phase are present. This condition is associated with the presence of anti-insulin antibodies that cause postprandial

Table 2 Medical treatment of hyperinsulinemic hypoglycaemia (HH) according to the pathology

Cause of HH	Treatments	References
Benign insulinoma	Diazoxide (from 100 to 600 mg up to 1500 mg per day)	Gill et al. [34]
	Somatostatin analogues	Vezzosi D et al. [36]
	Steroids	De Herder WW et al. [33]
Malignant insulinoma	Everolimus	Bernard et al. [55]
	Sunitinib	De herder WW et al. [56]
	Chemotherapy	Eriksson et al. [80]
	Peptide receptor radionuclide therapy (PRRT)	Baudin et al. [62]
Nesidioblastosis	Diazoxide, octreotide, alpha-glucosidase inhibitors (acarbose) or calcium channel blockers (verapamil and nifedipine)	Kapoor et al. [124]
Hirata syndrome	Steroids (prednisone, 30–60 mg/day)	Wong et al. [135]
	Plasmapheresis	Yaturu et al. [136]
Autoimmune hypoglycaemia type B	Steroids (prednisone 80 mg/day), azathioprine (100 mg/day)	Chon et al. [138]
	Combination of rituximab, cyclophosphamide and pulse steroids	Malek et al. [140]

hyperglycaemia; as the glucose levels decrease the insulin bound to antibodies is released, resulting in inappropriately high free insulin concentration that causes hypoglycaemia [128]. Systemic lupus erythematosus, benign monoclonal gammopathy and multiple myeloma are often associated. Methimazole treatment may be associated with the disease [129, 130]. In Hirata syndrome, the insulin levels are elevated, usually above 100 $\mu\text{U/mL}$, such as C-peptide and proinsulin, and insulin antibodies show a high percentage of binding to insulin [131]. Type B insulin resistance syndrome is characterized by severe hyperglycaemia, acanthosis nigricans and fasting hypoglycaemia episodes. The anti-insulin receptor antibodies are the cause of this syndrome, and it is more frequent in black young women [132]. At low titres, the antibodies act as partial agonists resulting in hypoglycaemia; at high titres they downregulate the receptor's response to insulin causing hyperglycaemia [133]. In this syndrome insulin levels, C-peptide and proinsulin are moderately elevated, and insulin receptor antibodies are present [126]. Type B insulin resistance is often associated with rheumatologic and hematologic diseases. Currently, there are nonstandard therapies for treating autoimmune forms of hypoglycaemia. In Hirata syndrome, a spontaneous remission of hypoglycaemia can be observed within 3–6 months of diagnosis. Anyway in this syndrome the response to therapy is usually good [134]. The first treatment is based on small frequent meals low in carbohydrate to prevent postprandial hypoglycaemia. Steroids, in particular oral prednisone (30–60 mg/day), would seem to solve the symptoms of hypoglycaemia [135]. Other therapeutic options such as acarbose (to decrease glucose absorption),

diazoxide and octreotide have demonstrated partial benefit in the management of this syndrome. The pancreatectomy should be considered in the presence of intractable hypoglycaemia [126]. A case of Hirata syndrome treated with plasmapheresis was reported, showing the regression of hypoglycaemia and the gradual disappearance of antibodies within a few months [136]. In type B insulin resistance the therapeutic approach is more complex and not fully understood, and the treatment is based on steroid therapy or immunosuppressant agents [137]. The improvement of hypoglycaemia, and the decrease in antibodies, in a patient with type B insulin resistance, after a first line of treatment with high dose of steroids (prednisone 80 mg/day), followed by the addition of azathioprine (100 mg/day) and the gradually steroids reduction (7.5 mg/day) [138] was reported. Arioglu et al. [139] reviewed the long-term clinical course of type B insulin resistance syndrome and concluded that the most effective treatment of type B insulin is a short-term high steroid dose therapy. A new therapeutic protocol was reported with an intensive combination of rituximab, cyclophosphamide and pulse corticosteroids, showing after 8 months of the treatment the remission of symptoms [140].

Conclusions

A correct differential diagnosis, mainly with the rarest forms of HH, is fundamental to perform an adequate treatment and to avoid unnecessary surgical treatment. When a benign insulinoma has been diagnosed, surgery is the first option,

with the mini-invasive approach, whenever possible. The management of malignant insulinoma is often multimodal and aimed to symptom and tumour control. Everolimus can represent the main treatment in refractory hypoglycaemic syndrome control, regardless of the anti-neoplastic response and insulin levels. Diet and medical therapy of hyperinsulinemia may provide relief in the most part of patients with suspected nesidioblastosis, even though for those patients who fail medical therapy, the surgical treatment with pancreatectomy or the conversion to a restrictive form of bariatric procedure should be recommended. Autoimmune forms of hypoglycaemia are uncommon, therapies are complex, and the results in the literature are controversial. However, if spontaneous remission is possible for Hirata syndrome, steroid and immunosuppressive agents may be considered the most effective therapy for type B insulin resistance.

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