J Endocrinol Invest
DOI 10.1007/s40618-016-0536-3

REVIEW

The treatment of hyperinsulinemic hypoglycaemia in adults: an update

M. V. Davi′[1] · A. Pia[2] · V. Guarnotta[3] · G. Pizza[4] · A. Colao[4] · A. Faggiano[5] · On behalf of NIKE Group

Received: 25 February 2016 / Accepted: 17 August 2016

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

✉ M. V. Davi′
mariavittoria.davi@ospedaleuniverona.it

1 Section of Endocrinology, Medicina Generale e Malattie Aterotrombotiche e Degenerative, Department of Medicine, University of Verona, Piazzale LA Scuro, Policlinico G.B. Rossi, 37134 Verona, Italy

2 Internal Medicine I, Department of Clinical and Biological Sciences, University of Turin, San Luigi Hospital, Orbassano, Italy

3 Section of Endocrinology, Biomedical Department of Internal and Specialist Medicine (DIBIMIS), University of Palermo, Palermo, Italy

4 Endocrinology Unit, Department of Clinical Medicine and Surgery, University of Naples Federico II, Naples, Italy

5 Thyroid and Parathyroid Surgery Unit, Istituto Nazionale per lo Studio e la Cura dei Tumori "Fondazione G. Pascale" IRCCS, Naples, Italy

Published online: 13 September 2016

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 um 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]. NIHPS 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 tumourous 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 μU/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 addiction 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.

Acknowledgments We would like to acknowledge the Nike Group: Manuela Albertelli, Emanuela Arvat, Roberto Baldelli, Alfredo Berruti, Antonio Bianchi, Lisa Bodei, Gerardo Botti, Francesco Corcione, Gianfranco Delle Fave, Laura De Marinis, Gaetano De Rosa, Antonella Di Sarno, Alessandra Dicitore, Nicola Fazio, Giuseppe Fanciulli, Piero Ferolla, Diego Ferone, Angelina Filice, Marco Gallo, Carla Giordano, Dario Giuffrida, Andrea Lania, Secondo Lastoria, Francesco Logoluso, Paola Loli, Pasqualino Malandrino, Marco Manzoni, Massimo Marchetti, Chiara Martini, Erika Messina, Roberta Modica, Cecilia Motta, Mauro Papotti, Stefano Partelli, Giovanni Persico, Alessandro Piovesan, Alfredo Pontecorvi, Valeria Ramundo, Paola Razzore, Francesca Rota, Francesco Scavuzzo, Concetta Sciammarella, Giovanni Vitale, Maria Chiara Zatelli.

Compliance with ethical standards

Conflict of interest M.V.D., A.P., V.G., G.P. declare that there is no conflict of interest. A.F. received speaker fees from Novartis and Ipsen; A.C. received research grants from Novartis, received speaker fees from Novartis and Ipsen and is a member of Novartis and Ipsen Advisory Board.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No informed consent.

References

1. Kaltsas GA, Besser GM, Grossman AB (2004) The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 25:458–511
2. Grimaldi F, Fazio N, Attanasio R et al (2014) Italian Association of Clinical Endocrinologists (AME) position statement: a stepwise clinical approach to the diagnosis of gastroenteropancreatic neuroendocrine neoplasms. J Endocrinol Invest 37:875–890
3. Cryer PE, Axelrod L, Grossman AB, Heller SR, Montori VM, Seaquist ER, Service FJ, Endocrine Society (2009) Evaluation and management of adult hypoglycemic disorders: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 94:709–728
4. Service FJ, McMahon MM, O'Brien PC, Ballard DJ (1991) Functioning insulinoma—incidence, recurrence and long term survival of patient: a 60-year study. Mayo Clin Proc 66:711–719
5. Service FJ (1999) Classification of hypoglycaemic disorders. Endocrinol Metab Clin N Am 28:501–517
6. Placzkowski KA, Vella A, Thompson GB, Grant CS, Reading CC, Charboneau JW, Andrews JC, Lloyd RV, Service FJ (2009) Secular trends in the presentation and management of functioning insulinoma at the Mayo Clinic, 1987–2007. J Clin Endocrinol Metab 94:1069–1073
7. Anlauf M, Wieben D, Perren A et al (2005) Persistent hyperinsulinemic hypoglycaemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol 9:524–533
8. Partelli S, Maurizi A, Tamburrino D, Baldoni A, Polenta V, Crippa S, Falconi M (2014) GEP-NETS update: a review on surgery of gastro-entero-pancreatic neuroendocrine tumors. Eur J Endocrinol 171:153–162
9. Davi MV, Falconi M (2009) Pancreas: insulinoma-new insights into an old disease. Nat Rev Endocrinol 5:300–302
10. Lopez CL, Albers MB, Bollmann C, Manoharan J, Waldmann J, Fendrich V, Bartsch DK (2016) Minimally invasive versus open pancreatic surgery in patients with multiple endocrine neoplasia type 1. World J Surg 40:1729–1736
11. Fernandez Ranvier GG, Shouhed D, Inabnet WB III (2016) Minimally invasive techniques for resection of pancreatic neuroendocrine tumors. Surg Oncol Clin N Am 25:195–215
12. Norton JA, Fang TD, Jensen RT (2006) Surgery for gastrinoma and insulinoma in multiple endocrine neoplasia type 1. J Natl Compr Canc Netw 4:148–153
13. Crippa S, Zerbi A, Boninsegna L, Capitanio V, Partelli S, Balzano G, Pederzoli P, Di Carlo V, Falconi M (2012) Surgical management of insulinomas: short- and long-term outcomes after enucleations and pancreatic resections. Arch Surg 147:261–266
14. Berends FJ, Cuesta MA, Kazemier G, van Eijck CH, de Herder WW, van Muiswinkel JM, Bruining HA, Bonjer HJ (2000) Laparoscopic detection and resection of insulinomas. Surgery 128:386–391
15. Nikfarjam M, Warshaw AL, Axelrod L, Deshpande V, Thayer SP, Ferrone CR, Fernández-del Castillo C (2008) Improved contemporary surgical management of insulinomas: a 25-year experience at the Massachusetts General Hospital. Ann Surg 247:165–172
16. Goh BK, Ooi LL, Cheow PC, Tan YM, Ong HS, Chung YF, Chow PK, Wong WK, Soo KC (2009) Accurate preoperative localization of insulinomas avoids the need for blind resection and reoperation: analysis of a single institution experience with 17 surgically treated tumors over 19 years. J Gastrointest Surg 13:1071–1077
17. Lo CY, Lam KY, Kung AW, Lam KS, Tung PH, Fan ST (1997) Pancreatic insulinomas: a 15-year experience. Arch Surg 132:926–930
18. Boukhman MP, Karam JH, Shaver J, Siperstein AE, Duh QY, Clark OH (1998) Insulinoma: experience from 1950 to 1995. West J Med 169:98–104
19. Cougard P, Goudet P, Peix JL, Henry JF, Sarfati E, Proye C, Calender A (2000) Insulinomas in multiple endocrine neoplasia type 1. Report of a series of 44 cases by the multiple endocrine neoplasia study group. Ann Chir 125:118–123
20. Giudici F, Nesi G, Brandi ML, Tonelli F (2012) Surgical management of insulinomas in multiple endocrine neoplasia type 1. Pancreas 41:547–553
21. Fernández-Cruz L, Martínez I, Cesar-Borges G, Astudillo E, Orduña D, Halperin I, Sesmilo G, Puig M (2005) Laparoscopic

surgery in patients with sporadic and multiple insulinomas associated with multiple endocrine neoplasia type 1. J Gastrointest Surg 9:381–388
22. Vezzosi D, Cardot-Bauters C, Bouscaren N, Lebras M, Bertholon-Grégoire M, Niccoli P, Levy-Bohbot N, Groussin L, Bouchard P, Tabarin A, Chanson P, Lecomte P, Guilhem I, Carrere N, Mirallié E, Pattou F, Peix JL, Goere D, Borson-Chazot F, Caron P, Bongard V, Carnaille B, Goudet P, Baudin E (2015) Long-term results of the surgical management of insulinoma patients with MEN1: a Groupe d'étude des Tumeurs Endocrines (GTE) retrospective study. Eur J Endocrinol 172:309–319
23. Mehrabi A, Fischer L, Hafezi M, Dirlewanger A, Grenacher L, Diener MK, Fonouni H, Golriz M, Garoussi C, Fard N, Rahbari NN, Werner J, Büchler MW (2014) A systematic review of localization, surgical treatment options, and outcome of insulinoma. Pancreas 43:675–686
24. Butturini G, Damoli I, Crepaz L, Malleo G, Marchegiani G, Daskalaki D, Esposito A, Cingarlini S, Salvia R, Bassi C (2015) A prospective non-randomised single-center study comparing laparoscopic and robotic distal pancreatectomy. Surg Endosc 29:3163–3170
25. Pai M, Habib N, Senturk H, Lakhtakia S, Reddy N, Cicinnati VR, Kaba I, Beckebaum S, Drymousis P, Kahaleh M, Brugge W (2015) Endoscopic ultrasound guided radiofrequency ablation, for pancreatic cystic neoplasms and neuroendocrine tumors. World J Gastrointest Surg 7:52–59
26. Rossi S, Viera FT, Ghittoni G, Cobianchi L, Rosa LL, Siciliani L, Bortolotto C, Veronese L, Vercelli A, Gallotti A, Ravetta V (2014) Radiofrequency ablation of pancreatic neuroendocrine tumors: a pilot study of feasibility, efficacy, and safety. Pancreas 43:938–945
27. Procházka V, Hlavsa J, Andrašina T, Starý K, Můčková K, Kala Z, Válek V (2012) Laparoscopic radiofrequency ablation of functioning pancreatic insulinoma: video case report. Surg Laparosc Endosc Percutan Tech 22:312–315
28. Limmer S, Huppert PE, Juette V, Lenhart A, Welte M, Wietholtz H (2009) Radiofrequency ablation of solitary pancreatic insulinoma in a patient with episodes of severe hypoglycaemia. Eur J Gastroenterol Hepatol 21:1097–1101
29. Akhlaghpoor S, Dahi F, Alinaghizadeh M, Shabestari AA (2011) CT fluoroscopy-guided transcaval radiofrequency ablation of insulinoma. J Vasc Interv Radiol 22:409–410
30. Peppa M, Brountzos E, Economopoulos N, Boutati E, Pikounis V, Patapis P, Economopoulos T, Raptis SA, Hadjidakis D (2009) Cardiovasc Interv Radiol 32:807–811
31. Rott G, Biggemann M, Pfohl M (2008) Embolization of an insulinoma of the pancreas with trisacryl gelatin microspheres as definitive treatment. Cardiovasc Interv Radiol 31:659–662
32. Levy MJ, Thompson GB, Topazian MD, Callstrom MR, Grant CS, Vella A (2012) US-guided ethanol ablation of insulinomas: a new treatment option. Gastrointest Endosc 75:200–206
33. de Herder WW, Niederle B, Scoazec JY, Pauwels S, Kloppel G, Falconi M, Kwekkeboom DJ, Oberg K, Eriksson B, Wiedenmann B, Rindi G, O'Toole D, Ferone D, Frascati Consensus Conference, European Neuroendocrine Tumor Society (2006) Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology 84:183–188
34. Gill GV, Rauf O, MacFarlane IA (1997) Diazoxide treatment for insulinoma: a national UK survey. Postgrad Med J73:640–641
35. Hirshberg B, Cochran C, Skarulis MC, Libutti SK, Alexander HR, Wood BJ, Chang R, Kleiner DE, Gorden P (2005) Malignant insulinoma: spectrum of unusual clinical features. Cancer 104:264–272
36. Vezzosi D, Bennet A, Courbon F, Caron P (2008) Short- and long-term somatostatin analogue treatment in patients with hypoglycaemia related to endogenous hyperinsulinism. Clin Endocrinol (Oxf) 68:904–911
37. Vezzosi D, Bennet A, Rochaix P, Courbon F, Selves J, Pradere B, Buscail L, Susini C, Caron P (2005) Octreotide in insulinoma patients: efficacy on hypoglycaemia, relationships with Octreoscan scintigraphy and immunostaining with anti-sst2A and anti-sst5 antibodies. Eur J Endocrinol 152:757–767
38. Stehouwer CD, Lems WF, Fischer HR, Hackeng WH, Naafs MA (1989) Aggravation of hypoglycaemia in insulinoma patients by the long-acting somatostatin analogue octreotide (sandostatin). Acta Endocrinol 121:34–40
39. Healy ML, Dawson SJ, Murray RM, Zalcberg J, Jefford M (2007) Severe hypoglycaemia after long-acting octreotide in a patient with an unrecognized malignant insulinoma. Intern Med J 37:406–409
40. de Sá SV, Corrêa-Giannella ML, Machado MC, de Souza JJ, Pereira MA, Patzina RA, Siqueira SA, Machado MC, Giannella-Neto D (2006) Somatostatin receptor subtype 5 (SSTR5) mRNA expression is related to histopathological features of cell proliferation in insulinomas. Endocr Relat Cancer 13:69–78
41. Bertherat J, Tenenbaum F, Perlemoine K, Videau C, Alberini JL, Richard B, Dousset B, Bertagna X, Epelbaum J (2003) Somatostatin receptors 2 and 5 are the major somatostatin receptors in insulinomas: an in vivo and in vitro study. J Clin Endocrinol Metab 88:5353–5360
42. Portela-Gomes GM, Stridsberg M, Grimelius L, Rorstad O, Janson ET (2007) Differential expression of the five somatostatin receptor subtypes in human benign and malignant insulinomas—predominance of receptor subtype 4. Endocr Pathol 18:79–85
43. Proye C, Malvaux P, Pattou F, Filoche B, Godchaux JM, Maunoury V, Palazzo L, Huglo D, Lefebvre J, Paris JC (1998) Noninvasive imaging of insulinomas and gastrinomas with endoscopic ultrasonography and somatostatin receptor scintigraphy. Surgery 124:1134–1143
44. Hay N, Sonenberg N (2004) Upstream and downstream of mTOR. Genes Dev 18:1926–1945
45. Fiebrich HB, Siemerink EJ, Brouwers AH, Links TP, Remkes WS, Hospers GA, de Vries EG (2011) Everolimus induces rapid plasma glucose normalization in insulinoma patients by effects on tumor as well as normal tissues. Oncologist 16:783–787
46. Yao JC, Shah MH, Ito T, RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group et al (2011) Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 364:514–523
47. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, Scoazec JY, Salazar R, Sauvanet A, Kianmanesh R, Barcelona Consensus Conference Participants (2012) ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 95:98–119
48. Oberg K (2011) Neuroendocrine tumors: recent progress in diagnosis and treatment. Endocr Relat Cancer 18(Suppl 1):S17–S25
49. Vergès B, Cariou B (2015) mTOR inhibitors and diabetes. Diabetes Res Clin Pract 110:101–108
50. Yao JC, Lombard-Bohas C, Baudin E et al (2010) Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 28:69–76
51. Kulke MH, Bergsland EK, Yao JC (2009) Glycemic control in patients with insulinoma treated with everolimus. N Engl J Med 360:195–197
52. Ong GS, Henley DE, Hurley D, Turner JH, Claringbold PG, Fegan PG (2010) Therapies for the medical management of

persistent hypoglycaemia in two cases of inoperable malignant insulinoma. Eur J Endocrinol 162:1001–1008
53. Ferrer-García JC, Tolosa-Torréns M, Hernando-Meliá C, Arribas-Palomar L, Sánchez-Juan C (2011) Everolimus resolving hypoglycaemia, producing hyperglycemia, and necessitating insulin use in a patient with diabetes and nonresectable malignant insulinoma. Endocr Pract 17:17–20
54. Thomas NJ, Brooke AM, Besser GM (2013) Long-term maintenance of normoglycaemia using everolimus in a patient with disseminated insulinoma and severe hypoglycaemia. Clin Endocrinol 78:799–800
55. Bernard V, Lombard-Bohas C, Taquet MC, Caroli-Bosc FX, Ruszniewski P, Niccoli P, Guimbaud R, Chougnet CN, Goichot B, Rohmer V, Borson-Chazot F, Baudin E, French Group of Endocrine Tumors (2013) Efficacy of everolimus in patients with metastatic insulinoma and refractory hypoglycaemia. Eur J Endocrinol 168:665–674
56. De Herder WW, van Schaik E, Kwekkeboom D, Feelders RA (2011) New therapeutic options for metastatic malignant insulinomas. Clin Endocrinol (Oxf) 75:277–284
57. Baratelli C, Brizzi MP, Tampellini M, Scagliotti GV, Priola A, Terzolo M, Pia A, Berruti A (2014) Intermittent everolimus administration for malignant insulinoma. Endocrinol Diabetes Metab Case Rep 2014:140047
58. Oberg K (2012) Biotherapies for GEP-NETs. Best Pract Res Clin Gastroenterol 26:833–841
59. Raymond E, Dahan L, Raoul JL et al (2011) Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 364:501–513
60. Lee Y, Jung HS, Choi HJ, Kim MJ, Kim TM, Park KS, Kim SY (2011) Life-threatening hypoglycaemia induced by a tyrosine kinase inhibitor in a patient with neuroendocrine tumor: a case report. Diabetes Res Clin Pract 93:e68–e70
61. Chen J, Wang C, Han J et al (2013) Therapeutic effect of sunitinib malate and its influence on blood glucose concentrations in a patient with metastatic insulinoma. Expert Rev Anticancer Ther 13:737–743
62. Baudin E, Caron P, Lombard-Bohas C, Société française d'endocrinologie; Groupe d'étude des tumeurs endocrines et al (2013) Malignant insulinoma: recommendations for characterisation and treatment. Ann Endocrinol (Paris) 74:523–533
63. Berruti A, Pia A, Terzolo M (2011) Advances in pancreatic neuroendocrine tumor treatment. N Engl J Med 364:1871–1872
64. Rinke A, Krug S (2016) Neuroendocrine tumours—medical therapy: biological. Best Pract Res Clin Endocrinol Metab 30:79–91
65. Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, Öberg K, Pavel M, Perren A, Toumpanakis C, O'Connor J, O'Toole D, Krenning E, Reed N, Kianmanesh R (2016) ENETS consensus guidelines update for neuroendocrine neoplasms of the jejunum and ileum. Neuroendocrinology 103:125–138
66. Maiche AG, Pyrhönen S, Mäki-Hokkonen H (1992) Treatment response to natural leukocyte interferon-alpha in relapsing malignant insulinoma with severe hypoglycaemia. Acta Oncol 31:365–366
67. Cives M, Kunz PL, Morse B, Coppola D et al (2015) Phase II clinical trial of pasireotide long-acting repeatable in patients with metastatic neuroendocrine tumors. Endocr Relat Cancer 22:1–9
68. Kumar U, Sasi R, Suresh S et al (1999) Subtype-selective expression of the five somatostatin receptors (hSSTR1-5) in human pancreatic islet cells: a quantitative double-label immunohistochemical analysis. Diabetes 48:77–85
69. Lamberts SW, de Herder WW, Hofland LJ (2002) Somatostatin analogs in the diagnosis and treatment of cancer. Trends Endocrinol Metab 13:451–457
70. Quinn TJ, Yuan Z, Adem A, Geha R, Vrikshajanani C, Koba W, Fine E, Hughes DT, Schmid HA, Libutti SK (2012) Pasireotide (SOM230) is effective for the treatment of pancreatic neuroendocrine tumors (PNETs) in a multiple endocrine neoplasia type 1 (MEN1) conditional knockout mouse model. Surgery 152:1068–1077
71. Walls GV, Stevenson M, Soukup BS, Lines KE, Grossman AB, Schmid HA, Thakker RV (2016) Pasireotide therapy of multiple endocrine neoplasia type 1-associated neuroendocrine tumors in female mice deleted for an Men1 allele improves survival and reduces tumor progression. Endocrinology 157:1789–1798
72. Tirosh A, Stemmer SM, Solomonov E, Elnekave E, Saeger W, Ravkin Y, Nir K, Talmor Y, Shimon I (2016) Pasireotide for malignant insulinoma. Hormones (Athens) 15:271–276
73. Moertel CG, Hanley JA, Johnson LA (1980) streptozotocin alone compared with streptozotocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 303:1189–1194
74. Cheng PN, Saltz LB (1999) Failure to confirm major objective antitumor activity for streptozotocin and doxorubicin in the treatment of patients with advanced islet cell carcinoma. Cancer 86:944–948
75. Delaunoit T, Ducreux M, Boige V, Dromain C, Sabourin JC, Duvillard P, Schlumberger M, de Baere T, Rougier P, Ruffie P, Elias D, Lasser P, Baudin E (2004) The doxorubicin-streptozotocin combination for the treatment of advanced well-differentiated pancreatic endocrine carcinoma; a judicious option? Eur J Cancer 40:515–520
76. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, Yao JC (2004) Fluorouracil, doxorubicin, and streptozotocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 22:4762–4771
77. Turner NC, Strauss SJ, Sarker D et al (2010) Chemotherapy with 5-fluorouracil, cisplatin and streptozotocin for neuroendocrine tumours. Br J Cancer 102:1106–1112
78. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, Helm J, Kvols L (2011) First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer J 117:268–275
79. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG (2001) Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 12:1139–1143
80. Eriksson B, Annibale B, Bajetta E, Mitry E, Pavel M, Platania M, Salazar R, Plöckinger U, Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society (2009) ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: chemotherapy in patients with neuroendocrine tumors. Neuroendocrinology 90:214–219
81. Dussol AS, Joly MO, Vercherat C, Forestier J, Hervieu V, Scoazec JY, Lombard-Bohas C, Walter T (2015) Gemcitabine and oxaliplatin or alkylating agents for neuroendocrine tumors: comparison of efficacy and search for predictive factors guiding treatment choice. Cancer 121(19):3428–3434
82. Sarmiento JM, Que FG, Grant CS, Thompson GB, Farnell MB, Nagorney DM (2002) Concurrent resections of pancreatic islet cell cancers with synchronous hepatic metastases: outcomes of an aggressive approach. Surgery 132:976–982
83. Touzios JG, Kiely JM, Pitt SC, Rilling WS, Quebbeman EJ, Wilson SD, Pitt HA (2005) Neuroendocrine hepatic metastases: does aggressive management improve survival? Ann Surg 241:776–783 **(discussion 783–785)**
84. Modlin IM, Lye KD, Kidd M (2003) A 5-decade analysis of 13,715 carcinoid tumors. Cancer 97:934–959
85. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, Anlauf M, Wiedenmann B, Salazar R (2012)

Barcelona Consensus Conference participants: ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 95:157–176
86. Lombardi M, De Lio N, Funel N, Sardella C, Russo D, Urbani C, Rossi G, Campani D, Martino E, Marcocci C, Boggi U, Bogazzi F (2015) Prognostic factors for pancreatic neuroendocrine neoplasms (pNET) and the risk of small non-functioning pNET. J Endocrinol Investig 38:605–613
87. Venook AP (1999) Embolization and chemoembolization therapy for neuroendocrine tumors. Curr Opin Oncol 11:38–41
88. Strosberg JR, Cheema A, Kvols LK (2011) A review of systemic and liver-directed therapies for metastatic neuroendocrine tumors of the gastroenteropancreatic tract. Cancer Control 18:127–137
89. Chamberlain RS, Canes D, Brown KT et al (2000) Hepatic neuroendocrine metastases: does intervention alter outcomes? J Am Coll Surg 190:432–445
90. Jakobs TF, Paprottka P, Hoffmann R et al (2010) ^{90}Yttrium radioembolization of symptomatic, unresectable neuroendocrine hepatic metastases. In: Society of interventional radiology (SIR) 35th annual scientific meeting. J Vasc Interven Radiol
91. Berwaerts J, Verhelst J, Hubens H et al (1997) Role of hepatic arterial embolisation in the treatment of malignant insulinoma. Report of two cases and review of the literature. Acta Clin Belg 52:263–274
92. Winkelbauer FW, Niederle B, Graf O et al (1995) Malignant insulinoma: permanent hepatic artery embolization of liver metastases—preliminary results. Cardiovasc Interv Radiol 18:353
93. Starke A, Saddig C, Mansfeld L, Koester R, Tschahargane C, Czygan P, Goretzki P (2005) Malignant metastatic insulinoma-postoperative treatment and follow-up. World J Surg 29(6):789–793
94. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH et al (2008) Treatment with the radiolabeled somatostatin analog (177 Lu-DOTA 0, Tyr3)octreotate: toxicity, efficacy, and survival. J Clin Oncol 26:2124–2130
95. Toumpanakis C, Caplin ME (2013) Update on the role of somatostatin analogs for the treatment of patients with gastroenteropancreatic neuroendocrine tumors. Semin Oncol 40:56–68
96. Van Schaik E, van Vliet EI, Feelders RA, Krenning EP, Khan S, Kamp K, Valkema R, van Nederveen FH, Teunissen JJ, Kwekkeboom DJ, de Herder WW (2011) Improved control of severe hypoglycaemia in patients with malignant insulinomas by peptide receptor radionuclide therapy. J Clin Endocrinol Metab 96(11):3381–3389
97. Costa R, Bacchi CE, Almeida Filho P (2013) Metastatic insulinoma managed with radiolabeled somatostatin analog. Case Rep Endocrinol 2013:252–259
98. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G, Reed N, Kianmanesh R, Jensen RT (2016) ENETS Consensus Guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 103:153–1571
99. Laidlaw GF (1938) Nesidioblastoma, the islet tumor of the pancreas. Am J Pathol 14:125–134
100. Kloppel G, Anlauf M, Raffel A, Perren A, Knoefel WT (2008) Adult diffuse nesidioblastosis: genetically or environmentally induced? Hum Pathol 39:3–8
101. Service FJ, Natt N, Thompson GB, Grant CS, van Heerden JA, Andrews JC, Lorenz E, Terzic A, Lloyd RV (1999) Noninsulinoma pancreatogenous hypoglycaemia: a novel syndrome of hyperinsulinemic hypoglycaemia in adults independent of mutations in Kir6.2 and SUR1 genes. J Clin Endocrinol Metab 84:1582–1589
102. Service FJ (1993) Clinical review 42: hypoglycaemias. J Clin Endocrinol Metab 76:269–272
103. Wiesli P, Brändle M, Schmid C, Krähenbühl L, Furrer J, Keller U, Spinas GA, Pfammatter T (2004) Selective arterial calcium stimulation and hepatic venous sampling in the evaluation of hyperinsulinemic hypoglycaemia: potential and limitations. J Vasc Interv Radiol 15:1251–1256
104. Reinecke-Lüthge A, Koschoreck F, Klöppel G (2000) The molecular basis of persistent hyperinsulinemic hypoglycaemia of infancy and its pathologic substrates. Virchows Arch 436:1–5
105. Glaser B (2000) Hyperinsulinism of the newborn. Semin Perinatol 24:150–163
106. Raffel A, Krausch MM, Anlauf M, Wieben D, Braunstein S, Klöppel G, Röher HD, Knoefel WT (2007) Diffuse nesidioblastosis as a cause of hyperinsulinemic hypoglycaemia in adults: a diagnostic and therapeutic challenge. Surgery 141:179–184
107. Kaplan EL, Rubenstein AH, Evans R, Lee CH, Klementschitsch P (1979) Calcium infusion: a new provocative test for insulinomas. Ann Surg 190:501–507
108. Service GJ, Thompson GB, Service FJ, Andrews JC, Collazo-Clavell ML, Lloyd RV (2005) Hyperinsulinemic hypoglycaemia with nesidioblastosis after gastric-bypass surgery. N Engl J Med 353:249–254
109. Shultz KT, Neelon FA, Nilsen LB, Lebovitz HE (1971) Mechanism of postgastrectomy hypoglycaemia. Arch Intern Med 128:240–246
110. Scavini M, Pontiroli AE, Folli F (2005) Asymptomatic hyperinsulinemic hypoglycaemia after gastric banding. N Engl J Med 353:2822–2823
111. Thaler JP, Cummings DE (2009) Minireview: hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. Endocrinology 150:2518–2525
112. Cummings DE (2005) Gastric bypass and nesidioblastosis—too much of a good thing for islets? N Engl J Med 353:300–302
113. Meier JJ, Bhushan A, Butler AE, Rizza RA, Butler PC (2005) Sustained beta cell apoptosis in patients with long-standing type 1 diabetes: indirect evidence for islet regeneration? Diabetologia 48:2221–2228
114. Meier JJ, Ritzel RA, Maedler K, Gurlo T, Butler PC (2006) Increased vulnerability of newly forming beta cells to cytokine-induced cell death. Diabetologia 49:83–89
115. Abellán P, Cámara R, Merino-Torres JF, Pérez-Lazaro A, del Olmo MI, Ponce JL, Rayón JM, Piñón F (2008) Severe hypoglycaemia after gastric bypass surgery for morbid obesity. Diabetes Res Clin Pract 79:e7–e9
116. Goldfine AB (2007) Changing horizons: approaches to diabetes care, current and future. Curr Opin Endocrinol Diabetes Obes 14:95–97
117. Clancy TE, Moore FD Jr, Zinner MJ (2006) Post-gastric bypass hyperinsulinism with nesidioblastosis: subtotal or total pancreatectomy may be needed to prevent recurrent hypoglycaemia. J Gastrointest Surg 10:1116–1119
118. Rumilla KM, Erickson LA, Service FJ, Vella A, Thompson GB, Grant CS, Lloyd RV (2009) Hyperinsulinemic hypoglycaemia with nesidioblastosis: histologic features and growth factor expression. Mod Pathol 22:239–245
119. Zgraggen K, Guweidhi A, Steffen R, Potoczna N, Biral R, Walther F, Komminoth P, Horber F (2008) Severe recurrent hypoglycaemia after gastric bypass surgery. Obes Surg 18:981–988
120. Habener JF (2002) The role of pancreatic duodenum homeobox protein-1 in the development of diabetes mellitus. Drug News Perspect 15:491–497

121. Won JG, Tseng HS, Yang AH, Tang KT et al (2006) Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS). Clin Endocrinol (Oxf) 65(5):566–578
122. Cui Y, Elahi D, Andersen DK (2011) Advances in the etiology and management of hyperinsulinemic hypoglycaemia after Roux-en-Y gastric bypass. J Gastrointest Surg 15:1879–1888
123. Vanderveen KA, Grant CS, Thompson GB, Farley DR, Richards ML, Vella A, Vollrath B, Service FJ (2010) Outcomes and quality of life after partial pancreatectomy for noninsulinoma pancreatogenous hypoglycaemia from diffuse islet cell disease. Surgery 148:1237–1245
124. Kapoor RR, James C, Hussain K (2009) Advances in the diagnosis and management of hyperinsulinemic hypoglycaemia. Nat Clin Pract Endocrinol Metab 5:101–112
125. Patti ME, McMahon G, Mun EC, Bitton A, Holst JJ, Goldsmith J, Hanto DW, Callery M, Arky R, Nose V, Bonner-Weir S, Goldfine AB (2005) Severe hypoglycaemia post-gastric bypass requiring partial pancreatectomy: evidence for inappropriate insulin secretion and pancreatic islet hyperplasia. Diabetologia 48:2236–2240
126. Lupsa BC, Chong AY, Cochran EK, Soos MA, Semple RK, Gorden P (2009) Autoimmune forms of hypoglycaemia. Medicine (Baltimore) 88:141–153
127. Uchigata Y, Hirata Y (1999) Insulin autoimmune syndrome (IAS, Hirata disease). Ann Med Intern (Paris) 150:245–253
128. Redmon JB, Nuttall FQ (1999) Autoimmune hypoglycaemia. Endocrinol Metab Clin N Am 28:603–618
129. Howard RL, Beck LK, Schneebaum A (1989) Systemic lupus erythematosus presenting as hypoglycaemia with insulin receptor antibodies. West J Med 151:324–325
130. Halsall DJ, Mangi M, Soos M, Fahie-Wilson MN et al (2007) Hypoglycaemia due to an insulin binding antibody in a patient with an IgA-kappa myeloma. J Clin Endocrinol Metab 92:2013–2016
131. Goldman J, Baldwin D, Rubenstein AH, Klink DD et al (1979) Characterization of circulating insulin and proinsulin-binding antibodies in autoimmune hypoglycaemia. J Clin Investig 63:1050–1059
132. Flier JS, Kahn CR, Roth J, Bar RS (1975) Antibodies that impair insulin receptor binding in an unusual diabetic syndrome with severe insulin resistance. Science 190:63–65
133. De Pirro R, Roth RA, Rossetti L, Goldfine ID (1984) Characterization of the serum from a patient with insulin resistance and hypoglycaemia. Evidence for multiple populations of insulin receptor antibodies with different receptor binding and insulin-mimicking activities. Diabetes 33:301–304
134. Paiva ES, Pereira AE, Lombardi MT, Nishida SK, Tachibana TT, Ferrer C, Hauache OM, Vieira JG, Reis AF (2006) Insulin autoimmune syndrome (Hirata disease) as differential diagnosis in patients with hyperinsulinemic hypoglycaemia. Pancreas 32:431–432
135. Wong SL, Priestman A, Holmes DT (2014) Recurrent hypoglycaemia from insulin autoimmune syndrome. J Gen Intern Med 29:250–254
136. Yaturu S, DePrisco C, Lurie A (2004) Severe autoimmune hypoglycaemia with insulin antibodies necessitating plasmapheresis. Endocr Pract 10:49–54
137. Yamasaki H, Yamaguchi Y, Fujita N, Kato C et al (2000) Anti-insulin receptor autoantibodies in a patient with type B insulin resistance and fasting hypoglycaemia. Acta Diabetol 37:189–196
138. Chon S, Choi MC, Lee YJ, Hwang YC, Jeong IK, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, Kim JW, Kim YS (2011) Autoimmune hypoglycaemia in a patient with characterization of insulin receptor autoantibodies. Diabetes Metab J 35:80–85
139. Arioglu E, Andewelt A, Diabo C, Bell M, Taylor SI, Gorden P (2002) Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance): a 28-year perspective. Medicine (Baltimore) 81:87–100
140. Malek R, Chong AY, Lupsa BC, Lungu AO, Cochran EK, Soos MA, Semple RK, Balow JE, Gorden P (2010) Treatment of type B insulin resistance: a novel approach to reduce insulin receptor autoantibodies. J Clin Endocrinol Metab 95:3641–3647