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REVIEW ARTICLE

Insulinoma After Bariatric Surgery: Diagnostic Dilemma and Therapeutic Approaches

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Abstract Hypoglycemia is increasingly recognized as a complication of bariatric surgery. Typically, hypoglycemia does not appear immediately postoperatively, but rather more than 1 year later, and usually occurs 1–3 h after meals. While rare, insulinoma has been reported after bariatric surgery. Clinical factors which should raise suspicion for insulinoma and the need for comprehensive clinical and biochemical evaluation include hypoglycemia occurring in the fasting state, predating bariatric surgery, and/or worsening immediately postoperatively, and lack of response to conservative therapy. Localization and successful resection of insulinoma can be achieved using novel endoscopic ultrasound and surgical approaches. In summary, hypoglycemia presenting shortly after gastric bypass or with a dominant fasting pattern should be fully evaluated to exclude insulinoma. Additionally, evaluation prior to gastric bypass should include screening for history of hypoglycemia symptoms.

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Background

Hypoglycemia is a rare but underappreciated complication of bariatric surgery and can be observed following both Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy [1, 2], as well as after other gastric procedures which either alter the pylorus or gastric emptying [3]. In most cases, post-bariatric hypoglycemia (PBH) appears to result from the collective effects of surgical alterations in alimentary flow, increases in incretin and insulin secretion [4–6], increased insulin-independent glucose disposal [7], alterations in systemic or intestinal metabolism [8–12], and additional factors not fully elucidated. In the majority of cases, hypoglycemia develops 1–3 years after surgery and is predominantly

postprandial in timing. Such a postprandial pattern is largely consistent with the intestinal mechanisms believed to contribute to the pathogenesis of this disorder. If these patterns are not observed, clinicians need to consider additional potential causes of hypoglycemia, including autonomous insulin secretion from an insulinoma. In this manuscript, we review published reports of insulinoma after bariatric surgery, frame the clinical diagnostic challenges in distinguishing insulinoma from post-bariatric hypoglycemia, and describe novel endoscopic approaches for successful localization and surgical resection of insulinoma.

Methods

In review of medical literature for insulinoma and hypoglycemia after gastric surgery, we searched using PubMed with key words "hypoglycemia," "gastric bypass," "gastric surgery," "bariatric surgery," "insulinoma," "pancreatic neuroendocrine tumor," and a combination of the above terms, including all dates up to January 15, 2016.

Data for the current patient with insulinoma and pancreatic neuroendocrine microadenoma were abstracted from the clinical health record.

Results

Hypoglycemia After Bariatric Surgery: Features and Differential Diagnosis

The diagnosis of hypoglycemia after bariatric surgery is challenging (Fig. 1), as symptoms may be nonspecific and variable in quality and intensity. Symptoms and signs may include adrenergic (palpitations, tremor, anxiety), cholinergic (sweating, hunger), and neuroglycopenic (confusion, falls, seizures, loss of consciousness) features. Compounding the clinical challenge is that many of these symptoms overlap with the dumping syndrome, a complication of some gastric surgical procedures. Therefore, it is critical to first determine whether symptoms are truly linked to hypoglycemia. Ideally, this would be accomplished by assessing plasma glucose levels at the time of symptoms. If this is not possible, home glucose monitoring using a glucometer or diagnostic continuous glucose monitor can be helpful as a first step to identify patterns. If glucose values are consistently normal at the time of symptoms, hypoglycemia is unlikely, and dumping syndrome or other cardiovascular causes of symptoms should be considered. If glucose values are low, clinicians still need to verify that Whipple's triad is fulfilled—symptoms,

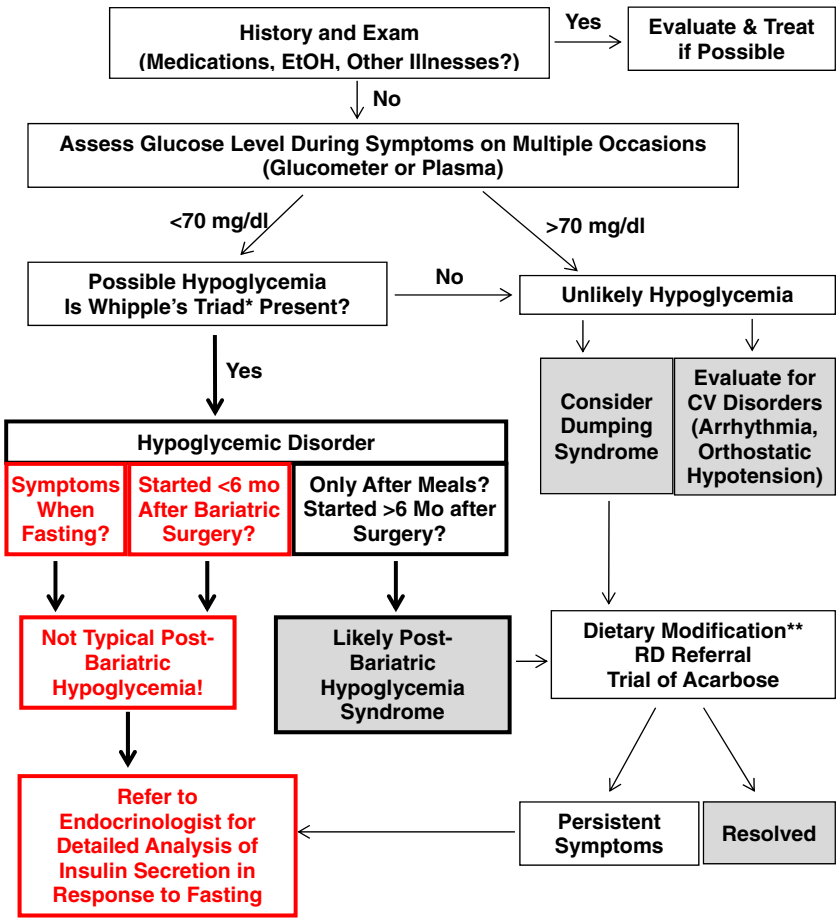

Fig. 1 Suggested approach to evaluating hypoglycemia in otherwise healthy appearing individual with history of gastric surgery. *Whipple's triad includes (1) symptoms, (2) plasma glucose <55 mg/dl, and (3) improvement of symptoms with normalization of blood glucose, **Controlled portions of complex carbohydrates, adequate protein, and healthy fats with micronutrient supplements

verification of low plasma glucose at the time of symptoms, and resolution of symptoms with elevation of glucose—before diagnosing a hypoglycemic disorder.

Once hypoglycemia has been verified, evaluation should be initiated in order to achieve a specific diagnosis. Detailed history should focus on symptoms, medications, alcohol intake, and other medical illnesses, and the timing of hypoglycemia episodes in relationship to meals, exercise, and fasting. Post-bariatric hypoglycemia typically presents with postprandial hypoglycemia, usually 2–4 h after meals. By contrast, fasting hypoglycemia or hypoglycemia not related to meal ingestion (occurring more than 4 h after eating) should raise suspicion for another etiology of hypoglycemia, such as autonomous secretion of insulin by an insulinoma or other hormonal or metabolic disorders (Supplemental Table 2). Thus, careful review of medications and consideration of other medical illnesses which could contribute to hypoglycemia should be performed (Table 1). It is also important to consider conditions which can mimic the symptoms of hypoglycemia, such as dumping syndrome, postural orthostatic tachycardia syndrome, anxiety, and adrenal insufficiency.

Workup of hypoglycemia should be performed in a stepwise manner, beginning with biochemical analysis of hormonal responses to spontaneous hypoglycemia to determine whether or not hypoglycemia is associated with inappropriately increased insulin levels. If this cannot be accomplished, provocative studies are required. Traditional approaches include either overnight outpatient fasting (if history suggests, this can be accomplished safely) or prolonged inpatient fasting, with measurements of insulin, C-peptide, β-hydroxybutyrate, and the counterregulatory hormones cortisol and glucagon. It is critical to recognize that hypoglycemia should be associated with full suppression of insulin levels; insulin levels that are not fully suppressed (may even be in the "normal" range) are abnormal when accompanied by hypoglycemia. If hyperinsulinemic hypoglycemia is documented in the postprandial state, but insulin secretion is normal in the fasting state, this pattern is consistent with post-bariatric hypoglycemia. If autonomous insulin secretion is identified (i.e., nonsuppressed in the fasting state), insulinoma needs to be considered, and anatomical localization was pursued in preparation for surgical resection, as detailed below.

Table 1 Differential diagnosis of hypoglycemia in an otherwise healthy appearing individual

Differential diagnosis of hypoglycemia	
Pancreatic/neuroendocrine:	Accidental hypoglycemia:
Post-bariatric hypoglycemia syndrome	Insulin overdose/abuse
Insulinoma	Insulin secretogogue overdose/abuse (sulfonylureas, meglitinides)
GLP1-producing tumor	Unripe ackee fruit poisoning
Noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS)	Ethanol
Insulin autoimmune disorder:	Other:
Antibody to insulin	Exercise-induced or other congenital hyperinsulinemia syndromes
Antibody to insulin receptor	Adrenal insufficiency

Insulinoma After Gastric Surgery

Review of the medical literature reveals a total of seven cases of insulinoma and one pancreatic neuroendocrine tumor reported in patients following various types of gastric surgery (Table 2). We now include an additional patient with an insulinoma and pancreatic neuroendocrine microadenoma who presented with symptoms of shakiness, blurred vision, lip numbness, cold sweats, and anxiety in response to fasting, meals, and exercise. Symptoms worsened progressively during the first month after gastric bypass surgery, but in retrospect had been present for several years preoperatively, based on fasting glucose levels (Supplemental Table 1A). Biochemical evaluation demonstrated hypoglycemia provoked by both fasting and exercise, with minimum glucose 44 mg/dl, inappropriately elevated insulin, proinsulin, and C-peptide, and suppressed beta-hydroxybutyrate (Supplemental Table 1B), indicating excessive and autonomous insulin secretion. Localization of presumed insulinoma was ultimately achieved using endoscopic ultrasonography (EUS) with Optison™ (Fig. 2a/b) and computed tomography arteriography (Fig. 2c). EUS-guided fine needle aspiration identified neoplastic epithelioid cells consistent with a well-differentiated, low grade (grade 1) neuroendocrine tumor. Surgical resection was performed with a minimally invasive approach. Intraoperative localization was achieved by identification of the reaction to the prior needle aspiration (Fig. 2d) and by intraoperative ultrasound. Given the patient's post-bypass hormonal milieu and risk for islet hyperplasia, robot-assisted distal pancreatectomy and splenectomy were performed instead of a pancreas-sparing procedure such as central pancreatectomy or enucleation [13]. Pathologic examination showed a 2.1-cm, well-differentiated neuroendocrine tumor, diffusely immunoreactive for insulin (Fig. 3) as well as a second well-circumscribed incidental microadenoma (0.28 cm), which was negative for insulin but positive for synaptophysin. The islets in the background non-neoplastic pancreas showed increased islet density in some areas and a few islets >400 μm in size (up to 440 μm), possibly representing early islet hyperplasia (Fig. 3). The significance of these findings is uncertain, as the average islet size was 197 μm (50 islets counted), and heterogeneity in islet distribution has been previously reported; there were no overt abnormalities in islet cell nuclear size or morphology [14].

Table 2 Pancreatic neuroendocrine tumors causing hypoglycemia in patients with history of gastric surgery

Author	Gender	Age	Surgery	Symptom onset	Pre-surgical BMI (kg/m^2)	Symptoms	Diagnosis
Zagury [43]	F	65	Fobi-Capella Gastric bypass	–	48.8		Insulinoma
Service [44]	F	54	RYGB	2 years after surgery	–	Confusion, 1–3-h postprandial	Insulinoma and multiple islet cell tumors
Abellan [45]	M	51	Vertical gastroplasty and intestinal bypass	6 months after surgery	55.8	Neuroglycopenia, loss of consciousness, seizure with fasting	Insulinoma and nesidioblastosis
Iglesias [18]	F	45	Bilateral truncal vagotomy and pyloroplasty	20 years after surgery	–	Sweating, tremor, weakness, and dizziness with fasting >8 h	Insulinoma and nesidioblastosis
Sato [46]	F	61	Total gastrectomy	Early after surgery	–	Dizziness with fasting and postprandial	Insulinoma
Seshadri [19]	F	61	Laparoscopic gastric banding	Preoperatively; evaluated 2 months post-operatively	45	Sweating, weakness and fatigue with fasting	Insulinoma
Guimaraes [47]	F	54	RYGB	2 years after surgery	42	Postprandial sweating and fainting	Glucagon-predominant, insulin/GLP1/somatostatin peptide containing pancreatic neuroendocrine tumor
Koca [48]	M	71	Antrectomy and loop gastrojejunostomy	Preoperatively		Fatigue, sweating, and unconsciousness with fasting	Insulinoma
Mulla (current report)	F	45	RYGB	Preoperatively	40	Shakiness, blurred vision, lip numbness, cold sweats, and anxiety with fasting and in postprandial and exercise-induced states	Insulinoma, neuroendocrine microadenoma

Review of the literature reporting insulinoma and pancreatic neuroendocrine tumors diagnosed following gastric surgery reveals that seven of patients (78 %) were women, a higher proportion as compared with 135 of 237 patients (57 %) with insulinoma who had no history of bariatric surgery [15]. This female predominance is likely reflective of the higher percentage of female bariatric patients [16]. Mean age of post-bariatric insulinoma patients was 56, an age similar to that for non-bariatric insulinoma patients in the large Mayo Clinic series [15].

In all nine patients, insulinoma was not initially considered as a likely diagnosis due to both its rarity and the predominance of non-fasting hypoglycemia in patients with history of gastric surgery. Not surprisingly, seven patients were unsuccessfully treated for dumping syndrome before further diagnostic evaluation led to the diagnosis of insulinoma. While typical post-bariatric hypoglycemia syndrome is characterized by postprandial timing of hypoglycemia, it is interesting that bariatric patients with insulinoma had a distinct pattern; 78 % had hypoglycemia in the fasting period—56 % exclusively when fasting and 22 % during both fasting and postprandial periods (Fig. 4). This pattern is similar to the Mayo Clinic case series of sporadic insulinoma [15] in which 94 % of patients presented with symptoms during the fasting state (73 % exclusively fasting), and 21 % had symptoms in both the fasting and postprandial states [15]. Given the mixed patterns, it is clear that timing does not provide a specific diagnostic clue. Collectively, these data underscore the current Endocrine Society guidelines indicating that evaluation of insulin secretion is needed in any patient with documented hypoglycemia [17]. However, fasting hypoglycemia in a post-bariatric patient is highly atypical; thus, diagnostic efforts should be particularly aggressive and focused to exclude insulinoma. Moreover, we recommend that even postprandial hypoglycemia in a post-bariatric patient which is refractory to first-level dietary and medical management should be considered for additional biochemical evaluation to exclude insulinoma (Fig. 1, Supplemental Table 2).

While insulinomas are commonly associated with weight gain, this pattern may be difficult to discern in the post-bariatric population. Bariatric patients with insulinomas or neuroendocrine tumors had diminished weight loss, stabilized weight, or even weight gain despite bariatric surgery [18, 19]. In fact, the one patient with insulinoma discovered after gastric banding gained weight despite four band-tightening procedures [19]. These patterns are reminiscent of the weight gain often observed in patients with sporadic insulinoma [20], attributed to both the anabolic effects of insulin and the need for increased food intake to treat hypoglycemia. Weight regain is common in the post-bariatric patient [21], potentially in relation to gut mucosal hypertrophy and GLP2 secretion [22, 23] and is thus not specific for excessive insulin secretion. Nevertheless, we suggest that weight gain or reduced weight

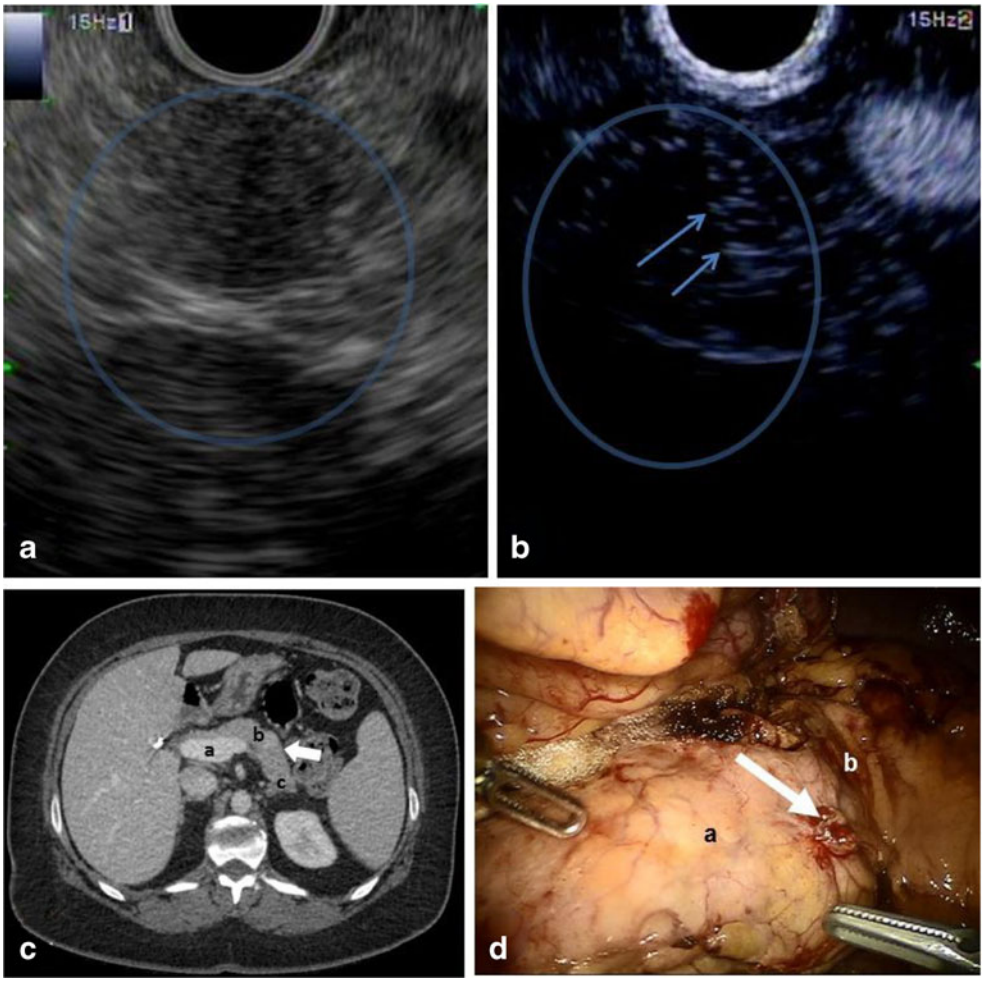

Fig. 2 Endoscopic ultrasonography of the pancreas demonstrating the insulinoma. **a** Ill-defined hypoechoic density within the pancreas parenchyma as seen on B-mode ultrasound. **b** Image demonstrates contrast-enhanced harmonics and shows rapid uptake of Optison™ contrast (Perflutren Protein-Type A Microspheres Injectable Suspension) seen as multiple hyperechoic foci (marked with *arrows*) within the lesion. Washout of contrast leaves a hypoechoic lesion without defined borders. **c** Computed tomography angiogram (pancreas protocol) demonstrates a subtle hyperattenuating 1.4 × 1.7-cm mass at the pancreatic body-tail junction. Labels: *a* portal vein, *b* pancreatic body, *c* pancreatic tail. *Arrow* indicates mass. **d** Intraoperative inspection of the pancreas. The puncture site on the pancreatic parenchyma from prior biopsy is indicated by the *arrow*. *a* pancreatic body, *b* pancreatic tail

loss in a bariatric patient with symptoms of hypoglycemia, especially in the fasting state, should prompt consideration of further evaluation.

Preoperative Localization of Insulinoma After Gastric Surgery

Localization of insulinoma is often challenging and even more so in post-gastric surgery patients. Preoperative localization reduces the risk of reoperation for missed lesions and prevents blind resection associated with increased risk for perioperative adverse events and postoperative diabetes [24–26]. Although intraoperative inspection and palpation of the pancreas may be justified in resource-constrained environments [26], failure rates for intraoperative detection range between 10–27 % [27].

With the introduction of thin-section, multidetector contrast-enhanced imaging, computed tomography (CT) has been increasingly employed for localization of insulinoma [28]. The sensitivity of CT is dependent on the vascular phase and section thickness. Although enhancement is seen in both the arterial and portal-venous phases, the normal pancreatic parenchyma enhances in the venous phase, making contrast between tumor and normal tissue greater during the arterial phase. Detection rates for insulinoma in arterial and portal-venous phase images are 88.2 and 11.8 %, respectively [26, 28]. Similarly, the sensitivity of dual-phase helical CT with thin sections (3.2 mm) is superior (94.4 %) to standard techniques (57.1 %) [26]. This difference is attributed to the small size of insulinoma, with 66–90 % measuring less than 2 cm [24, 26, 29]. MRI detects insulinoma with 73–95 % sensitivity; improvements are attributed to the introduction of diffusion-weighted imaging [27].

Endoscopic ultrasonography has 80–92 % sensitivity for detecting insulinoma as small as 5 mm [25, 27], and EUS-guided fine needle aspiration allows pathologic confirmation in 57 % [25]. Combining EUS with either CT or MRI improves the sensitivity for insulinoma detection to nearly 100 %. If EUS, CT, and MRI fail to detect a tumor, selective arteriography and intra-arterial calcium stimulation with hepatic venous sampling can be performed. These radiologic procedures have the highest sensitivity, but are invasive and should be used only as a last resort [24, 25, 30].

Despite the success of EUS imaging for insulinoma, EUS has not been widely implemented in post-RYGB patients, as

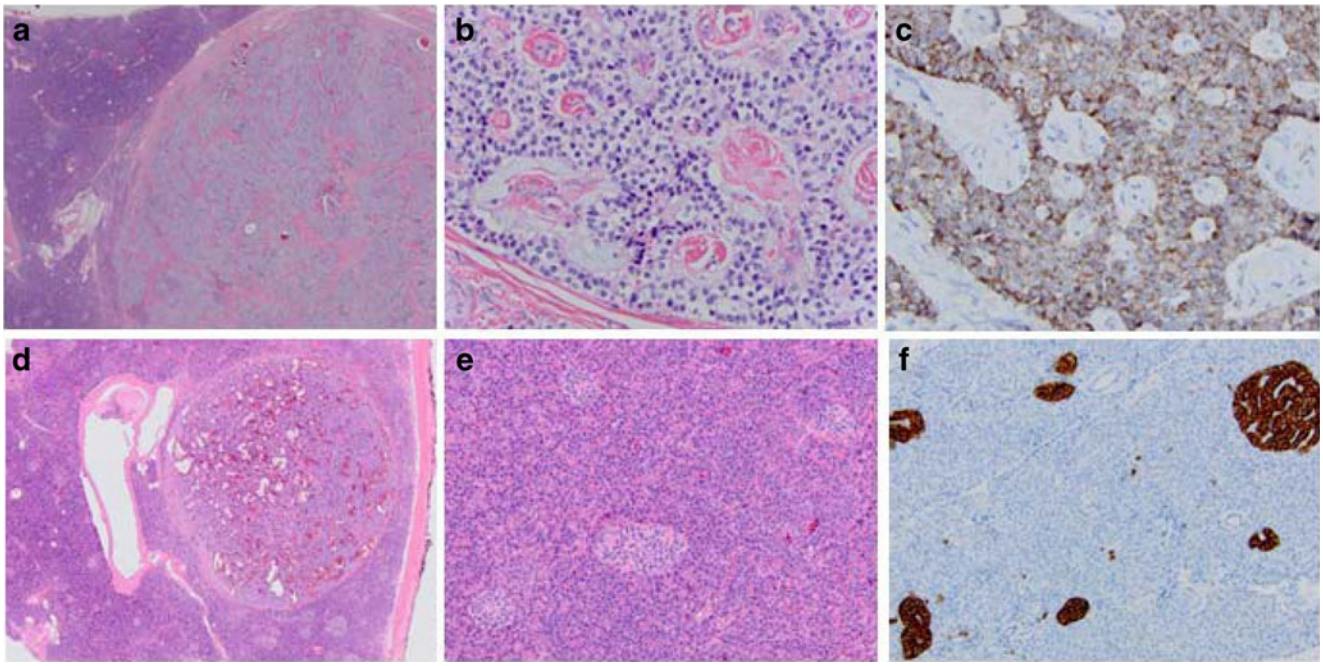

Fig. 3 Histopathology of the resected pancreatic sample, including insulinoma (**a**–**c**), neuroendocrine microadenoma (**d**), and background pancreas (**e**–**f**). **a** Well-differentiated, low-grade neuroendocrine tumor showing a well-circumscribed nodule composed of nests of epithelioid cells within fibrous stroma (tumor on right, non-neoplastic pancreas on left), 20× magnification, H&E. **b** 400× magnification, H&E. **c** 400× magnification, insulin immunostain. **d** Neuroendocrine microadenoma. Well-circumscribed nodular proliferation of neuroendocrine cells measuring up to 2.8 mm (right), 40× magnification, H&E. **e** Islets showing some variability in distribution and size, 200× magnification, H&E. **f** Synaptophysin immunostain, 200× magnification

accessing the proximal duodenum to image the pancreatic head and common bile duct can be difficult. However, imaging of the pancreatic body and tail and FNA biopsies can be safely obtained using a trans-pouch approach [31]. In our patient, localization of the insulinoma remained occult until successful EUS imaging with Optison [32].

Intraoperative Localization, Surgical Techniques, and Outcomes

Recent studies indicate superior short-term recovery and equivalent long-term outcomes after minimally invasive pancreatic resection compared to open pancreatic surgery [33–35]. Localization during minimally invasive resection is critical to successful tumor clearance as the homogeneity of the retroperitoneal fat and decreased tactile feedback pose a challenge to intraoperative identification of lesions located deep in the pancreatic parenchyma. Preoperative fine needle tattooing via EUS reduces operative times during minimally invasive pancreatic resections and may minimize the risk of injury to surrounding structures [36]. In parallel, intraoperative ultrasonography (IOUS) can be used to evaluate tumor location, proximity to the main pancreatic duct, and involvement of the pancreatic duct and vasculature [26, 27, 33]. The sensitivity of IOUS is 85 % and is optimal when combined with palpation [26, 27]. Additionally, IOUS is important as preoperative confirmation of one insulinoma does not guarantee the absence of additional missed tumors [27, 33].

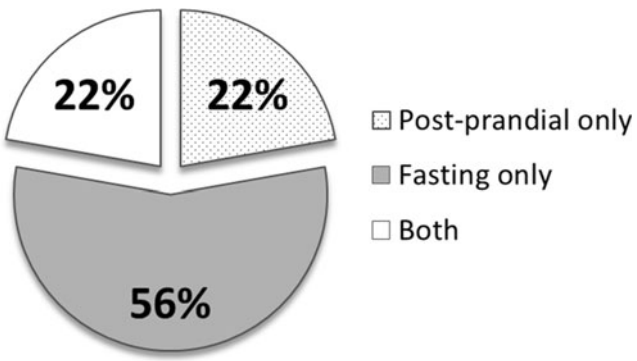

Fig. 4 Frequency of hypoglycemia occurring in the fasting state, postprandial state, or both in patients with insulinoma discovered following gastric surgery

Optimal surgical treatment of insulinoma requires complete resection [24]. This can be achieved by enucleation of smaller lesions which do not involve the main pancreatic duct, but may also require partial or total pancreatectomy depending on tumor location and multiplicity [33]. Multiple factors need to be considered prior to decision-making regarding optimal approach for an individual patient.

Operative time, blood loss, and hospital stay are not significantly different after enucleation or partial pancreatectomy [24]. Postoperative morbidity ranges from 25–41 % with a higher rate of pancreatic fistula after enucleation [24, 25,

27]; mortality ranges from 0–6 % [24, 33]. Enucleation is more likely to leave microscopic tumor at the surgical margin (33–38 %) as compared to distal pancreatectomy [24, 25]. However, positive resection margins are not associated with increased recurrence rates and have not adversely impacted survival up to 20 years (100, 100, and 93 % at 5, 10, and 20 years, respectively) [24, 25].

Retrospective comparisons of minimally invasive and open surgery have shown similar successful tumor resection rates (>95 %), operative times, complication, and fistula rates, but minimally invasive approaches are associated with shorter lengths of stay [33], decreased blood loss and transfusion rates, and improved cosmesis [35]. Conversion rates with laparoscopic surgery approach 30 %, often due to inability to locate the tumor when laparoscopic ultrasonography is not performed [37]. The robotic-assisted technique significantly reduces the conversion rate to <5 %, reduces morbidity, and is superior to the laparoscopic technique [34].

Resolution of hypoglycemia is achieved in the majority of patients undergoing surgery [25, 33]. However, among post-RYGB patients, hormone-mediated mechanisms contributing to hypoglycemia should be considered prior to decision-making regarding the optimal surgical approach for an individual patient. Functional increases in insulin secretion occur post-RYGB as a result of increased glucose sensitivity of the β-cell [5] and increased fasting and postprandial secretion of GLP1 and other incretins [7]. In addition, rapid delivery of nutrients to the small intestine due to accelerated gastric emptying or bypass or loss of pyloric function can also increase the stimulus for postprandial insulin secretion [38]. Initial reports suggested that increased islet mass might contribute to excessive insulin secretion in some patients; however, subsequent analyses indicated no increase in β-cell mass, indicating dominance of functional dysregulation of insulin secretion [14]. Although no data are available to address the required extent of pancreatectomy in patients with post-RYGB hypoglycemia, we suggest that partial pancreatectomy may be preferred over enucleation to permit evaluation of diffuse β-cell hyperplasia. Insulinoma occurring in patients who have had gastric surgery raises the possibility that the postoperative hormonal environment could contribute to increased β-cell proliferation in susceptible individuals. For example, the incretin hormone GLP1 is associated with islet proliferation in rodents [29, 39], and the combination of high plasma levels of GLP1 and abundant GLP1 receptors in insulinoma tissue [40] could promote increased insulin secretion, increased islet growth, and potential clonal expansion and eventual development of autonomy in susceptible patients. Available data do not allow us to address this possibility at present.

Assessing prevalence of insulinoma is not possible due to reporting bias (both incomplete and excessive when condition is rare), while diagnostic evaluation for hypoglycemia in the post-gastric surgery patient may result in increased diagnoses of insulinoma. Given that estimated population prevalence of insulinoma is four cases per one million person-years [41], one would predict 0.78 cases among the 193,000 bariatric surgical patients in the US annually [42]. While this perspective is somewhat reassuring, future longitudinal studies will be required to evaluate prevalence of insulinoma in this population.

Conclusion

In summary, insulinoma can occur following bariatric surgery. While insulinoma is rare, hypoglycemia presenting shortly after bariatric surgery or predominantly in the fasting states is highly atypical and thus, should be fully evaluated to exclude insulinoma. Additionally, we recommend that patients presenting for evaluation prior to bariatric surgery should be screened for history of hypoglycemia symptoms; if present, a complete endocrine evaluation should be considered to exclude hypoglycemia and define the extent of insulin secretion.

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Compliance with Ethical Standards

Conflict of Interest Authors CMM, AS, EUY, DL, MSS, and AJM declare no conflict of interest. MEP reports grants from American Society for Metabolic and Bariatric Surgery, Medimmune, Nuclea Biosciences, Bristol-Myers Squibb, Astra-Zeneca, Novo-Nordisk Foundation, and Sanofi outside the submitted work. In addition, Dr. Patti has a submitted patent "Methods and Compositions for Treating Hypoglycemia."

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

Informed Consent Does not apply to this review article.

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