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RESEARCH ARTICLE

# Severe Recurrent Hypoglycemia after Gastric Bypass Surgery

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**Abstract**
*Background* Bariatric surgery is, at present, the most effective method to achieve major, long-term weight loss in severely obese patients. Recently, severe recurrent symptomatic hyperinsulinemic hypoglycemia was described as a consequence of gastric bypass surgery (GBS) in a small series of patients with severe obesity. Pancreatic nesidioblastosis, a hyperplasia of islet cells, was postulated to be the cause, and subtotal or total pancreatectomy was the suggested treatment.
*Methods* We observed that severe, disabling hypoglycemia after GBS occurred only in patients with loss of restriction. Whether restoration of gastric restriction might treat severe, recurrent hypoglycemia after GBS is unknown.
*Results* Therefore, gastric restriction was restored by surgical placement of a silastic ring ($n$=8, first two patients with additional distal pancreatectomy) or an adjustable gastric band ($n$=4) around the pouch in 12 consecutive patients presenting with severe hypoglycemia (blood glucose below 2.2 mM). At follow-up after restoration of gastric restriction (median follow-up 7 months, range 5 to 19 months), 11 patients demonstrated no hypoglycemic episodes, while one had recurrence of hypoglycemia and underwent distal pancreatectomy. Procedural mortality was 0% and morbidity 8.3%.
*Conclusion* Patients suffering from severe recurrent hypoglycemia after GBS can be treated, in most cases, just by restoration of gastric restriction. Distal pancreatectomy should be considered a second-line treatment.

**Keywords** Gastric bypass · Gastric banding · Dumping · Nesidioblastosis · Hypoglycemia · Gastric restriction

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## Introduction

Obesity is a global epidemic that continues to accelerate despite the often extraordinary efforts to lose weight by afflicted individuals. It is one of the 10 leading US health indicators and is associated with an increased risk for cardiovascular disease, diabetes, and certain forms of cancer. A linear relation between the body mass index (BMI) and mortality has been demonstrated [1–6]. Within the adult US population surveyed in 2005, 60.5% of individuals were overweight, 32.2% were obese, and up to 5.3% were extremely obese [7, 8]. In Switzerland, the prevalence of overweight and that of obesity among adults were found to be 31% and 8%, respectively, and those among children were 20% and 7.4% [9]. The yearly direct medical expenditures attributable to such obesity figures are enormous [10].

At present, bariatric surgery is the most effective method to achieve major, long-term weight loss. The best operations reduce body weight by 35–40%, and most of this effect is maintained long-term [11–14]. Postsurgical weight

loss improves all obesity-related comorbidities and the net effect is an increase in quality of life and a decrease in overall mortality [12, 13, 15–17].

Recently, severe recurrent symptomatic hyperinsulinemic hypoglycemia was described as the consequence of gastric bypass surgery in a small series of patients with morbid obesity [18]. Pancreatic nesidioblastosis, a hyperplasia of islet cells, was postulated to be the cause of the disease. Accordingly, adaptive islet changes were described in the majority of the resected specimens. Subtotal pancreatectomy was the suggested treatment. Several reports of pancreatectomies have since supported the original concept [19–21].

We observed that severe, disabling hypoglycemia after gastric bypass surgery occurred in patients with loss of gastric restriction. Clinically, it is a severe form of a dumping syndrome. We demonstrate in this paper that restoration of gastric restriction, usually done by a laparoscopic approach, should be considered as the first-line treatment before pancreatectomy.

## Patients and Methods

### Patients

Twelve patients (10 women and 2 men; median age 41 years, ranging from 27 to 49 years) developed severe recurrent hypoglycemia 1.5–8.5 years after Roux-en-Y gastric bypass surgery and presented with repeated episodes of severe postprandial hypoglycemia. All patients had grade 1 or grade 2 hypoglycemia according to the classification below; the documented glucose levels in all patients were below 2.0 mmol/l. C-peptide and insulin levels were not measured at the time of hypoglycemia. Their mean BMI (±SD) was 44 (±2) kg/m$^2$ before gastric bypass surgery and 29 (±1) kg/m$^2$ at the time of evaluation. Patients were seen at 1 month after surgery and, thereafter, every 2 to 3 months by one of the authors. Loss of restriction was defined clinically by weight regain, increasing meal portion size, shorter duration of satiety and higher frequency of hunger feelings.

### Clinical Approach and Follow-up

Patients showing symptoms of potential recurrent hypoglycemia were screened using Sigstad's Score [22] and categorized as follows:

Grade 1: Plasma glucose levels <2.2 mmol/l with neuroglycopenic symptoms (seizures, paralyses, ataxia, loss of consciousness, aggressive behavior, and blurred vision; impairment of mental concentration, vision, speech, and memory)

Grade 2: Plasma glucose levels <2.2 mmol/l without neuroglycopenic symptoms. Patient shows general and adrenergic symptoms (nausea, dizziness, sweating, tremor, palpitations, tachycardia, and agitation)

Grade 3: Plasma glucose levels between 2.2 and 2.8 mmol/l with simultaneous adrenergic symptoms

Sigstad's Score was determined before and after surgical restoration of restriction to estimate clinical severity of postgastric bypass hypoglycemia (late dumping).

### Radiological Investigations

To rule out endocrine or exocrine pancreatic diseases, in particular, insulinoma, either magnetic resonance imaging or computerized tomography was carried out (Table 2). Furthermore, in four patients who were to undergo open surgery because of multiple previous abdominal procedures (two patients) or pancreatic resection (two patients), imaging was performed with intraoperative ultrasound (Table 2).

### Selective Arterial Calcium Stimulation Test with Hepatic Venous Sampling

For identification and regionalization of insulinoma or a hyperfunctional beta cell mass, a selective arterial calcium stimulation test (SACS) was performed in seven patients as originally described [23]. To rule out exogenous insulin consumption, both insulin and C-peptide were measured. A twofold or higher increase in insulin concentration in the right hepatic vein in the 30- or 60-s samples (or both) in response to the injection of 0.025 mEq of calcium per kilogram of body weight into the splenic, superior mesenteric, and gastroduodenal arteries was considered to indicate hyperfunctional beta cells in the vascular territory of the respective artery. Calcium injections were separated by periods of 15 min to allow hormone concentrations to return to baseline values.

A response after calcium infusion into the gastroduodenal or superior mesenteric artery was indicative of beta cell hyperfunction in the head and uncinate process of the pancreas; a response after splenic artery injection indicated beta cell hyperfunction in the body and tail of the pancreas. When no vascular territory was dominant, the response was considered nonlocalizing/diffuse.

### Surgical Procedures

#### *Surgical Techniques to Restore Gastric Restriction*

In all but four cases, a laparoscopic approach to the upper abdomen using five 12-mm troicarts was used. The area of the gastric pouch was freed from all adhesions and the gastrojejunostomy was exposed. The angle of His was freed

and the entrance to the lower mediastinum opened to rule out pouch formation above the diaphragm. A 30-French gastric tube was inserted transorally, the tip placed above the anastomosis. The jejunum below was clamped and the pouch size was outlined by insufflating air under pressure into the pouch. Pouches estimated as larger than 30 ml (not measured) were reduced to 10–15 ml (not measured) with a linear stapler. Then, in all small pouches, a perigastric dissection was made 1 cm above the anastomosis and a silastic ring (Bentec Medical, Woodland, CA, USA), according to Fobi [24], was inserted and closed with a circumference of 6–6.5 cm to a snug alignment ($n$=8, Table 2). In four cases, a pars flaccida tunnel was created and an adjustable gastric band (SAGB, Obtech Medical S.a.r.l., Le locle, Switzerland/Ethicon-Endo Surgery, Cincinnnati, OH, USA) was placed in a standard technique [25] because the perigastric dissection was considered to be too dangerous due to increased risk of injury to the pouch (Table 2).

In patients undergoing additional distal pancreatectomy through laparotomy, the resection line was chosen in the porto-mesenteric axis [26]. Intraoperatively, an ultrasound of the pancreas was performed to rule out preoperatively undetected small tumors. During laparoscopic procedures, no pancreatic biopsy was performed because risks were considered inappropriate. Before applying a surgical technique, all patients were seen by a nutritionist to optimize eating behavior for late dumping.

### Histopathology

Ellipsoid biopsies at the inferior edge of the pancreas were taken over the portal vein, in the pancreatic body, and in the tail. The biopsy sites were closed by fine nonabsorbable 4–0 monofilament stitches. All specimens were examined by the same pathologist (RB). A reference pathologist for endocrine diseases (PK) examined all specimens and biopsies. No interobserver variability was found.

The currently accepted major criteria and morphologic findings of adult diffuse nesidioblastosis include macroscopic, microscopic, and immunohistochemical exclusion of an insulinoma; multiple beta-cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm; islets with normal spatial distribution and regular hormone expression patterns of the various cell types; and no proliferative activity of endocrine cells. Minor histopathological diagnostic criteria include increased number of islets, lobulated islet structure, irregular shape and occasional enlargement of islets, and macronucleoli in beta-cells [27, 28]. The formalin-fixed tissue from biopsies and resection specimens was totally paraffin-embedded. The resection specimens were sectioned in 1-mm slices. The histological sections (3–4 μm) were stained with hematoxylin and eosin. Additional sections were immunostained with the following antibodies: insulin (mouse monoclonal, dilution 1:2,000, Diagnostic BioSystems, Pleasanton, CA, USA), glucagon (rabbit polyclonal, dilution 1:75, Cell Marque, Hot Springs, AR, USA), somatostatin (rabbit polyclonal, dilution 1:200, Cell Marque, Sierra, CA, USA), and MIB-1 (mouse monoclonal, dilution 1:100, DakoCytomation, Glostrup, Denmark).

### Statistics

Results are given as mean ± SD or median with range where appropriate. Comparisons before and after treatment were done using Mann–Whitney U test.

## Results

### Clinical Presentation and Investigation

Twelve patients (10 females, 2 males) presented with severe postprandial hypoglycemia at a median interval of 2 years (1–8.5 years) after gastric bypass surgery. Seven patients suffered from grade I symptoms (see "Patients and Methods" section) characterized by accidents and convulsions. Two of these patients were unable to ingest any calories while at work because of fear of unconsciousness. The remaining five patients had severe hypoglycemic grade II symptoms with documented plasma glucose levels below 2.2 mmol/l more than 90 min after initiation of their last meal. Sigstad's Score at time of diagnosis was 24±2 (Table 2).

The SACS test, performed in 7 of the 12 patients, was negative in one patient, demonstrated nonlocalizing/diffuse hyperstimulation in three patients, and demonstrated localizing/focal hyperstimulation in the tail/body of the pancreas in the three remaining patients. Correlation of SACS with histopathological findings was low in that SACS predicted histopathological results in only two out of five patients (Table 2).

In 11 out of 12 patients (Table 2), the possibility of an insulinoma was investigated by either a pancreas-specific CT or MRI scan. With the exception of one patient (Table 2), all scans were negative. MRI of this patient showed a suggestive 2-mm lesion (confirmed by intraoperative ultrasound), and SACS demonstrated an increase of insulin levels of more than sixfold. Histologically, adult pancreatic nesidioblastosis was found in this patient despite focal response on SACS, again demonstrating no accordance of histopathology and SACS (Tables 1 and 2).

### Histopathological Findings

In the first patient (Table 2) undergoing pancreatic resection, structural changes of the islets possibly corresponding

**Table 1** Patients characteristics

| Patient no. | Age (years) | Gender | Onset of hypoglycemia after GBS (years) | Severity score | Plasma glucose[a] |
|---|---|---|---|---|---|
| 1 | 49 | F | 8.5 | I | 1.5 |
| 2 | 27 | M | 1 | II | 2.1 |
| 3 | 36 | F | 3.5 | I | 1.9 |
| 4 | 39 | F | 5 | I | 1.8 |
| 5 | 47 | F | 1.5 | II | 2 |
| 6 | 64 | F | 2 | I | 1.8 |
| 7 | 48 | F | 1.5 | I | 1.8 |
| 8 | 48 | M | 3.5 | I | 1.7 |
| 9 | 41 | F | 2 | II | 1.8 |
| 10 | 49 | F | 2 | I | 1.8 |
| 11 | 59 | F | 2 | II | 1.8 |
| 12 | 39 | F | 3 | II | 1.9 |

*GBS* gastric bypass surgery
[a] Lowest measured plasma glucose level

to nesidioblastosis were suspected on frozen section. Detailed examination of the resected specimen, including reference pathology and imunohistochemistry, did not confirm an adult pancreatic nesidioblastosis.

The second patient (Table 2) with the focal lesion in the tail of the pancreas surprisingly did not have an insulinoma. The small lesion corresponded pathologically to a hamartoma-like lesion of the pancreas with ductal and islet proliferation (Fig. 1a). The islets outside the hamartoma-like lesion did have nesidioblastosis-like changes (Fig. 1b).

The pancreatic biopsies in the other two patients (Table 2) with open surgery did not demonstrate nesidioblastosis-like changes. Histopathological examination of those biopsies revealed normally structured pancreatic tissue with no evidence of an increased number of islets, which were homogenous in size and shape. Islet cells had a normal spatial distribution and regular hormone expression patterns of the various endocrine cell types. No proliferative activity (Ki-67 antigen) of endocrine cells was demonstrated. Accordingly, nesidioblastosis was not confirmed.

The pancreatic specimen of the patient with recurrent hypoglycemic episodes after restoration of restriction (Table 2), who underwent distal pancreatectomy in a follow-up operation 11 months after restoration of restriction, revealed structural changes of the islets possibly corresponding to nesidioblastosis suspected on frozen section. Detailed examination of the resection, including reference pathology and imunohistochemistry, confirmed the diagnosis of nesidioblastosis. An insulinoma was excluded.

## Outcome

Before restoration of restriction (median 2 years after gastric bypass), patients' weights increased by 8.7±1.9 kg

**Table 2** Pre- and postoperative investigations and findings

| Patient | CT | MRI | SACS | IOUS | Surgery | Nesidioblastosis | Sigstad's score | | Follow up (months) |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Pre-[a] | Post-[a] | |
| 1 | | − | Focal | − | Fobi and PR | No | 23 | 5 | 15; resolved |
| 2 | | + | Focal | + | Fobi and PR | Yes | 23 | 2 | 4; resolved |
| 3 | − | | Negative | − | Fobi and PBX | No | 23 | 6 | 15; resolved |
| 4 | | − | Diffuse | − | Fobi and PBX | No | 23 | 3 | 14; resolved |
| 5 | | − | Diffuse | | Fobi | | 23 | 8 | 9; resolved |
| 6 | | ND | | | Fobi | | 23 | 8 | 11; resolved |
| 7 | − | − | Focal | | Fobi | | 28 | 15 | 4; resolved |
| 8 | | − | Diffuse | − | AGB and PR[b] | Yes | 23 | 18 (4) | 15; resolved[b] |
| 9 | | − | | | AGB | | 19 | 7 | 18; resolved |
| 10 | | − | | | AGB | | 28 | 5 | 7; resolved |
| 11 | | − | | | AGB | | 23 | 5 | 6; resolved |
| 12 | | − | | | Fobi | | 23 | 9 | 6; resolved |

Distal pancreatectomy was performed 11 months after AGB implantation due to recurrence of severe hypoglycemia. The sign "–" represents done, with negative result; and "+" represents done, with a suggestive 2-mm lesion
*CT* computed tomography, *MRI* pancreas-specific magnetic resonance imaging, *SACS* selective arterial calcium stimulation test, *IOUS* intraoperative ultrasound, *ND* patient declined to have MRI due to panic disorder, *Fobi* silastic ring according Fobi [24], *PR* pancreatic left resection, *BX* pancreatic biopsy, *AGB* adjustable gastric band [28]
[a] Pre- and postrestoration of restriction
[b] Patient suffered from postoperative relapse of symptoms (Score 18) and underwent distal pancreatic resection. At 4 months, he was free of symptoms (Score 4)

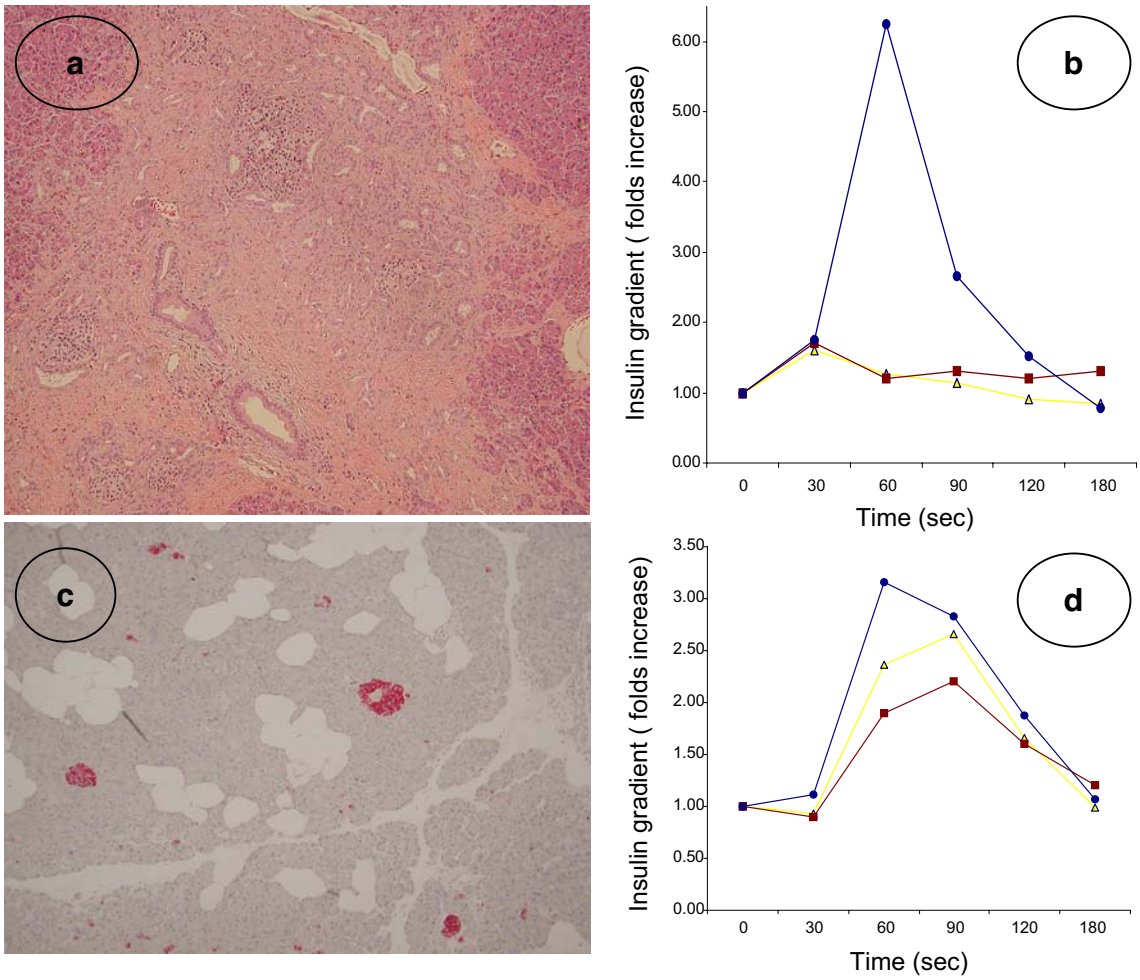


**Fig. 1** Histopathology and SACS. **a** Hematoxylin and eosin staining of pancreatic resection of patient No. 2 shows proliferation of ducts in correlation with islets. **b** SACS of the same patient shows focal positive response in the splenic artery indicating focal lesion in the pancreatic tail. **c** Immunohistochemistry staining of a biopsy that was taken from patient No.4. Islets (*red*) are normal in size and number. **d** SACS of the patient No. 4 shows a diffuse positive response

(1–27 kg). As expected, weight decreased at maximum follow-up by 10.1±1.1 kg (1.5–17.9 kg). Total mortality for all performed procedures was 0%, and morbidity was 8.3% (Table 2). At follow-up after 3 to 12 months, all patients were asymptomatic or significantly improved with respect to postprandial hypoglycemia and dumping symptoms. This clinical outcome is mirrored in the significant decrease in the Sigstad's Score from 24±2 at the time of diagnosis to 8±2 at last follow up ($p<0.01$, Table 2). In the first two patients, restoration of restriction and distal pancreatectomy were performed simultaneously. Thus, it remains unclear which of the two procedures prompted the observed relief of postprandial severe hypoglycemia. However, only 1 out of 10 patients (Table 1) treated with restoration of restriction developed recurrent severe grade I hypoglycemia due to severe solid food intolerance along with massive esophageal dilatation as a consequence of pouch banding. Therefore, in this patient, the adjustable band was removed and distal pancreatic resection (50–60% of the parenchyma) was done 11 months later. Four months after distal pancreatectomy, he was well and free of hypoglycemic symptoms (Sigstad's Score 4). Again, in this patient, it was not clear whether pancreatectomy or pouch banding was successful because the latter had to be abandoned for band complication. Patients who underwent pancreatic resection did not suffer from exocrine or endocrine pancreatic insufficiency (data not shown).

## Discussion

Recently, a severe recurrent symptomatic hypoglycemia was shown to occur as a consequence of gastric bypass surgery in a small series of patients with morbid obesity [18]. Subtotal or total pancreatectomy was suggested to be the treatment of choice for this condition [19–21]. Insulinoma, the most

common cause of hyperinsulinemic hypoglycemia in adults, was considered as a differential diagnosis and, in fact, was demonstrated in one of the six patients reported in that study. Structural changes of the endocrine pancreas resembling adult pancreatic nesidioblastosis, an exquisitely rare cause of hyperinsulinemic hypoglycemia, were postulated to be the underlying cause of the disabling clinical condition.

We observed that, in a small percentage of gastric bypass patients, a severe form of postprandial hypoglycemia occurred when gastric restriction was lost and gastric pouch emptying was too rapid. Thus, our hypothesis was that the patients suffered from a severe late dumping syndrome that is a consequence of reactive hypoglycemia from an exaggerated release of insulin that cannot be countered by a sustained glucose delivery [29]. A pathologic glucagon-like peptide-1 response may also play a role in hyperinsulinemic hypoglycemia in patients with late dumping syndrome. The recommendation of a pancreatic resection to correct a severe dumping syndrome seems to have too many inherent risks. In particular, the mortality of pancreatic resection in specialized units is 1–5%, with an associated total morbidity of 20–40% [26, 30] and an important risk for developing diabetes mellitus in particular in cases with an 80–90% resection as proposed for nesidioblastosis [31].

Our results demonstrate that recurrent severe hypoglycemia can usually be corrected by restoration of restriction either by implanting a fixed silastic ring according to Fobi or by placing an individually adjustable band around the gastric pouch. Effective restoration of restriction is demonstrated by the fact that weight increase during the period of late dumping was offset by the decrease in weight after reestablished restriction. In 9 out of 10 patients, postprandial hypoglycemia and its clinical sequels as assessed by Sigstad's Score (Table 2) resolved as a consequence of simple restoration of gastric restriction. In the majority of patients, these procedures can be performed laparoscopically. In this study, simple restoration of gastric restriction through laparoscopic operation was performed with no morbidity or mortality, thus comparing favorably to the anticipated 20–40% morbidity after pancreatic resection [26, 30].

Only 1 out of 10 patients (Table 1) treated with restoration of simple restriction developed recurrent grade I hypoglycemia due to severe solid food intolerance, along with massive esophageal dilatation as a consequence of pouch banding. Therefore, in this patient, the adjustable band was removed and a distal pancreatic resection (50–60% of the parenchyma) was done 11 months later. Four months after distal pancreatectomy, he was well and free of hypoglycemic symptoms (Sigstad's Score 4). Because the restriction of the pouch had to be abandoned for band complication, it remains unclear whether pancreatectomy or pouch banding prompted normalization of postprandial hypoglycemia in this patient. Interestingly, histopathological diagnoses revealed changes in line with pancreatic adult nesidioblastosis. Whether simple restoration of gastric restriction in the presence of adult pancreatic nesidioblastosis can be an adequate treatment of postprandial hypoglycemia remains an open question. Despite this uncertainty and because of its safety and high efficiency, we propose, in our algorithm herein (Fig. 2), laparoscopic restoration of gastric restriction as the first-line treatment of postprandial hypoglycemia unresponsive to nutritional counseling, as suggested by Bantle et al. [32].

This recommendation is further supported by the fact that adult pancreatic nesidioblastosis cannot be assessed through simple, noninvasive methods without invasive pancreatic biopsy. In our series, arterial calcium stimulation tests were not able preoperatively to predict adult nesidioblastosis. The preoperative predictive value of SACS in this small series was only 40% and should therefore be omitted as a

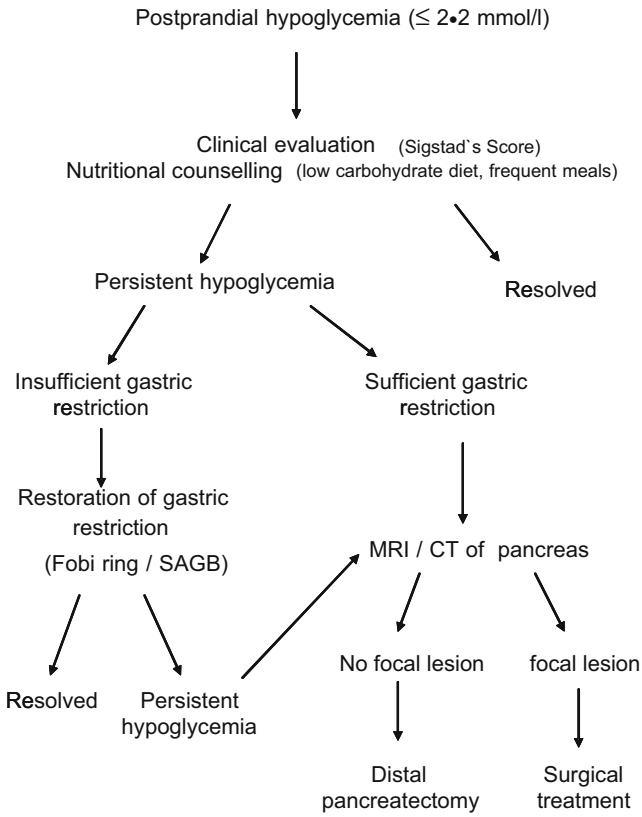


**Fig. 2** Proposed algorithm for investigating patients with severe postprandial hypoglycemia after gastric bypass surgery and loss of restriction

preoperative diagnostic tool. Thus, our algorithm, which includes SACS only exceptionally, should not only be safe but also cost-effective. Whether our results can be replicated in larger series of patients is an interesting and open question.

Our histopathological results are also in accordance with a recent report indicating that the control pancreata used in the original study of Meier and colleagues were obtained from pancreatic cancer patients [33], in whom insulin secretion is known to be disturbed [34]. Butler and colleagues performed additional morphometric analyses of the pancreatic tissue of the same patients and compared them with pancreata obtained at autopsy from individuals without known pancreatic diseases. In patients with postgastric bypass hypoglycemia, β-cell mass was not increased, and no evidence of increased islet neogenesis and β-cell replication or decreased β-cell loss was found compared with BMI-matched control subjects. However, mean β-cell nuclear diameter was greater in patients after gastric bypass surgery compared with lean and obese control subjects. This could indicate that the insulin secretory rate per β-cell was inappropriately high in patients after gastric bypass surgery.

We conclude that, in the majority of patients with severe postprandial hypoglycemia after gastric bypass who are unresponsive to adequate diet modifications, their symptoms can reliably be controlled by simple laparoscopic restoration of gastric restriction as the first-line surgical treatment, rather than pancreatic resection.

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