Hyperinsulinemic hypoglycemia following gastric bypass surgery for obesity
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Purpose of review
To examine the recently recognized association between bariatric surgery-induced weight loss and postprandial hyperinsulinemic hypoglycemia.

Recent findings
Postprandial hypoglycemia following gastric bypass for obesity is generally considered a late manifestation of the dumping syndrome and can usually be managed with dietary modification. A rare syndrome characterized by more severe postprandial hypoglycemia and hyperinsulinemia, accompanied by diffuse pancreatic islet hyperplasia and expansion of beta-cell mass, however, has recently been identified. In our experience, the therapeutic approach to these patients is guided by the severity and frequency of hypoglycemia, and includes nutritional modification to reduce postprandial glycemic excursion and stepped medical management, including acarbose, octreotide and diazoxide. Other therapeutic agents previously used to inhibit insulin secretion or action, including calcium channel blockade, β-blockers and anticholinergics, have been minimally effective. For life-threatening hypoglycemia refractory to medical management, partial pancreatectomy may be necessary, but hypoglycemia has recurred in some patients. These findings suggest that gastric bypass-induced weight loss may unmask an underlying beta-cell defect or contribute to pathologic islet hyperplasia.

Summary
Severe postprandial hyperinsulinemic hypoglycemia may be regarded as a rare, late complication of bariatric surgery. Management of these patients may require nutritional, pharmacological and, on occasion, surgical intervention. The pathophysiology remains incompletely understood.

Keywords
bariatric surgery, hyperinsulinemia, hypoglycemia, islet hyperplasia, obesity

Abbreviation
GLP-1 glucagon-like peptide 1

Introduction
Obesity is occurring at epidemic rates in the United States and worldwide. The prevalence of obesity in the United States in 2001 was 19.8% – an increase of 74% from the 1991 prevalence of 12%. This represented approximately 21.4 million obese men and 22.9 million obese women [1], at the time of the most recent census, and rates are continuing to rise. Unfortunately, medical management of obesity, including diet or medication, has met with limited success. In parallel, bariatric surgical procedures have become increasingly common as they may achieve sustained weight reduction of up to 50% of excess body weight in the majority of patients (reviewed in [2]), and are more effective than nonsurgical approaches [3]. Moreover, gastric bypass surgery produces rapid resolution of metabolic abnormalities associated with type 2 diabetes, even before major weight loss has been achieved [4]. The increasing prevalence of obesity and successes linked to bariatric surgery have led to a marked increase in surgical procedures, from 13,000 in 1998 to more than 130,000 in 2005 in the United States alone [5].

While the benefits of gastric bypass surgical procedures to improve weight and metabolic status are clear, there are associated complications. Short-term complications include pulmonary embolus, intestinal leak, wound infections and staple line failure. Recognized long-term complications include nutrient deficiencies, neuropathy and dumping syndrome. Dumping syndrome is caused by rapid gastric emptying into the jejunum and ileum, resulting in contact with partially digested foods, mechanical expansion and altered secretion of intestinal hormones (reviewed in [6] and [7]). Together, these changes may result in systemic volume contraction, adrenergic stimulation and late postprandial hypoglycemia. While dumping syndrome can usually be managed with dietary modification, rare cases of severe postprandial hypoglycemia refractory to dietary modification and medical management have recently been identified in patients following Roux-en-Y gastric bypass surgery [8**–9**]. In very severe cases, pancreatectomy has been required for control of insulin secretion; pancreatic...
pathology demonstrated diffuse islet hyperplasia and expansion of beta-cell mass, with no insulinomas. While severe symptomatic hypoglycemia is uncommon in proportion to the number of bariatric procedures performed, noninsulinoma hyperinsulinemic hypoglycemia in adults itself is rare. Thus, the frequency of hyperinsulinemic hypoglycemia after Roux-en-Y gastric surgery suggests an association. In this review, we describe the clinical presentation and management of patients with postbypass hyperinsulinemic hypoglycemia syndrome, and discuss potential mechanisms linking gastric bypass surgery to the development of hyperinsulinemic hypoglycemia.

**Presentation and differential diagnosis**

Patients with postbypass hyperinsulinemic hypoglycemia syndrome typically present 1–2 years following bariatric surgery and have had successful weight loss with the procedure. Symptoms of hypoglycemia include typical autonomic symptoms of palpitations, anxiety, sweating, hunger or paresthesias. Patients may also experience more severe neuroglycopenic symptoms of confusion, fatigue, loss of consciousness or seizures. Hypoglycemic episodes typically occur 1–3 h after meals, and become more frequent or severe over time.

Severe postprandial hyperinsulinemic hypoglycemia can be difficult to distinguish from dumping syndrome, which has been reported to develop in 10–15% of gastric bypass patients [10]. In contrast to the 1–2-year delay from surgery to the onset of symptoms with postprandial hyperinsulinemic hypoglycemia, dumping syndrome symptoms often begin shortly after the surgical procedure. Early dumping may begin during or immediately after a meal, and may include vasomotor and gastrointestinal complaints due to accelerated gastric emptying and intestinal transit, placing hyperosmolar nutrients in the jejunum and ileum, with resultant volume shifts. These fluid shifts have been associated with an exaggerated catecholamine response and hemoconcentration. Others have shown that dumping symptoms are associated with the rapid release of gut-derived hormones [11]. Symptoms of early dumping include nausea, vomiting, bloating, cramping, urgency to defecate, diarrhea, and fatigue. Some patients may also experience more severe symptoms of confusion or syncope as a result of volume shifts, which may occur up to 2 hours after the meal [12]. Alternatively, these symptoms may result from hypoglycemia, and may include weakness, palpitations, sweating, and dizziness. Avoidance of dietary carbohydrates and frequent, small meals is usually successful for the majority of patients with dumping syndrome.

Thus, while postprandial hypoglycemia in postbypass patients may be linked to the dumping syndrome, a small but distinct group of patients with severe hypoglycemia are distinguished by the severity of hypoglycemia with neuroglycopenia, including motor vehicle accidents or seizures; the delayed onset of hypoglycemia following surgery; and the relative lack of response to intensive dietary modification commonly recommended for patients with dumping, including frequent small meals, avoidance of simple carbohydrates and cornstarch supplementation. Additionally, in contrast to the patient with more typical dumping syndrome, early gastrointestinal symptoms tend to be mild.

The postgastric bypass hypoglycemia syndrome is most similar to the rare entity of noninsulinoma pancreaticogenous hypoglycemia (NIPH) described by Service et al. [13]. Five patients were identified with postprandial (not fasting) hypoglycemia. All had negative evaluation by both 72-h fast and radiographic studies, but a positive arterial calcium stimulation venous sampling test. Pancreatectomy to an extent suggested by the stimulation test was performed. Pathology revealed islet hyperplasia without insulinoma, and procedures were largely curative [14].

Insulinoma, either isolated or in the context of multiple endocrine neoplasia syndrome, must also be considered in the evaluation of postbypass hypoglycemia. While hyperinsulinemia related to insulinoma typically results in fasting hypoglycemia, postprandial hypoglycemia can occasionally be seen in patients with insulinomas. While insulinoma has been described in a single postbypass patient [15], we have observed diffuse insulin secretion in our patients with severe hypoglycemia, and have found no insulinomas despite careful pancreatic sectioning in those patients ultimately requiring pancreatectomy.

Other causes of hypoglycemia which could also play a pathogenic role in postbypass patients (reviewed in [16]) include: hormonal deficiencies, such as cortisol, glucagon, epinephrine, thyroid hormone, or growth hormone; altered secretion of vasoactive intestinal peptide (VIP), gastrin, parathyroid hormone (PTH) or related peptide (PTH-rP), serotonin or other neuroendocrine markers, including chromogranin A or urinary hydroxyindoleacetic acid (HIAA); surreptitious exogenous insulin or sulfonylurea use; drugs such as alcohol, quinine or lithium; renal or hepatic failure; deficient hepatic gluconeogenesis, whether nutritional or related to underlying enzymatic deficiency such as fructose 1,6 diphosphatase deficiency; nonislet cell tumor (e.g. secreting IGF-2); gastrointestinal dysmotility, leading to mismatch between insulin secretion and nutrient absorption; and, rarely, insulin autoantibodies [17]. To date, we have found no evidence linking any of these factors with postbypass hyperinsulinemic hypoglycemia. Serum VIP, gastrin, PTH and related peptide, chromogranin A, serotonin, urinary...
reduce initial insulin secretion and provide nutrient and snacks may further slow initial nutrient absorption, controlled in quantity. Addition of protein and fat to all meals glycemic load (such as found in whole grains) and con- by a large meal. Carbohydrates should be complex, low in insulin secretion. We recommend frequent small proceeded to stepped pharmacologic management as guided by the severity and frequency of hypoglycemia.

Therapeutic recommendations
The therapeutic approach to these patients should be guided by the severity and frequency of hypoglycemia. Treatment begins with medical nutritional therapy and proceeds to stepped pharmacologic management as needed. Dietary interventions aim to reduce stimulus for insulin secretion. We recommend frequent small meals to reduce the insulin secretory response generated by a large meal. Carbohydrates should be complex, low in glycemic load (such as found in whole grains) and controlled in quantity. Addition of protein and fat to all meals and snacks may further slow initial nutrient absorption, reduce initial insulin secretion and provide nutrient source following the peak of insulin. Cornstarch supple- contents, such as the ExtendBar, are useful and more palatable than cornstarch alone, and may be used in the morning, evening or both. If essential fatty acid deficiency is present, replacement is indicated.

Initial pharmacologic intervention might include α-glucosidase inhibitors, such as acarbose (Precose) or miglitol (Glyset), to reduce postprandial plasma glucose and stimulus for insulin secretion. These agents provide only modest protection from hypoglycemia and it is important to note that if hypoglycemia should occur, these agents may reduce the response to oral glucose.

Limited pharmacologic agents are available for use in humans to directly inhibit insulin release. Agents to inhibit insulin secretion include the K(ATP) channel ligand diazoxide and the somatostatin receptor agonist, octreotide. Diazoxide administration is the mainstay of medical therapy for neonatal hyperinsulinism and may be useful in adult patients [20]. While relatively well tolerated in the newborn population, diazoxide tolerance in the previously obese adult population may be limited by fluid retention, congestive heart failure and respiratory distress. Octreotide may initially be administered subcutaneously prior to meals and, if effective, may be converted to monthly intramuscular injection to reduce the difficulty for the patient associated with repetitive dosing. Diazoxide and somatostatin receptor antagonists may be tried in combination. Other therapeu- tic agents previously used to inhibit insulin secretion, including calcium channel blockers, β-blockers and anticholinergics, have been less effective due to patient intolerance or lack of efficacy, but further therapeu- tic trials may be warranted for individual patients. Likewise, glucagon infusion therapy has been successful in some patients with neonatal hyperinsulinism [21] and in patients with tumor-induced hypoglycemia [22] but, to date, has not been studied in patients with post bypass syndromes.

Some patients continue to have severe, life-threatening hypoglycemia despite medical nutritional and pharma- cologic management, and therefore must be considered for surgical management. Reversal of Roux-en-Y gastric bypass may be considered. We have observed increased severity and frequency of episodic hypoglycemia in one patient, however, despite surgical deconstruction of bypass anatomy and regain of nearly all of previously lost weight [8**]. While one cannot generalize from a single patient, this does suggest reversal of the gastric bypass may not be sufficient.

At present, surgical recommendation generally has been a partial pancreatectomy, with the extent of excision guided by the intra-arterial calcium stimulation venous
sampling test. Pancreatectomy is potentially a highly morbid procedure and should be reserved only for life-threatening and medically unresponsive hyperinsulinemic hypoglycemia. It is also important to recognize that some patients have had recurrence of hyperinsulinemic hypoglycemia, despite partial pancreatectomy guided by testing. Thus, in some, more extensive surgery including subtotal or total pancreatectomy may be necessary.

Pathology
Histopathology from surgical specimens has revealed diffuse islet hyperplasia with small and large islets, including areas of sheets of islets, with no evidence of insulinoma or neoplastic transformation (Fig. 1). Some islets have been noted to be adjacent to and budding from ducts – a finding consistent with the pathologic term ‘nesidioblastosis’. No general evidence of chronic pancreatitis exists. Beta-cell relative volume is increased compared to that seen in pancreas sections from lean or obese nondiabetic patients \[23,24\]. Importantly, both this increase in beta-cell relative volume and abnormal function (hyperinsulinemia) are inappropriate in these weight-reduced patients.

Potential pathophysiology mechanisms
At present, it remains unclear whether the patients who develop hyperinsulinemic hypoglycemia following Roux-en-Y bariatric surgery have a predisposition to this condition that predates the bariatric procedure, or whether the syndrome is a consequence of the altered metabolic milieu that follows the procedure (Fig. 2). Important potential mechanisms for islet hyperplasia include: an unrecognized familial or genetic hyperinsulinemia syndrome which may contribute to obesity and which is subsequently unmasked by the surgical weight loss and associated improved insulin sensitivity; reduced apoptosis of islets following weight loss that had previously expanded to compensate for obesity, leading to inappropriately high islet mass.

Figure 1 Hemotoxylin-and-eosin (H&E) staining of pancreatic tissue

Hemotoxylin-and-eosin (H&E) staining of pancreatic tissue from a normal pancreas (left) and from a patient with hyperinsulinemic hypoglycemia following gastric bypass (right) demonstrating hyperplasia of islets. Individual islets have relatively normal organization with regard to insulin and glucagon stain (not shown) but are increased in number, vary in size, occur in aberrant clusters and frequently surround ductal profiles (200X magnification).
relative to current insulin sensitivity; or stimulation of islet expansion by metabolic changes induced by gastric bypass surgery.

Familial hyperinsulinism may be found in adult family members of neonates diagnosed with persistent hyperinsulinemic hypoglycemia of infancy (PHHI). Mutations in the sulfonylurea receptor SUR1, the inwardly rectifying potassium channel inwardly rectifying potassium channel Kir6.2, glucokinase (GK), glutamate dehydrogenase and short-chain 3-hydroxyacyl CoA dehydrogenase account for the majority of cases. SUR1 mutations, usually inherited in an autosomal recessive pattern, tend to be more severe and may require pancreatectomy. Autosomal-dominant forms of familial hyperinsulinism which may be milder [25] have been linked to the GK gene in some families [26]. Additional familial forms are characterized by exercise-induced insulin secretion, but responsible mutation(s) have not been identified [27]. Thus, it is also possible that the weight loss induced by bariatric surgery and associated improvement in insulin sensitivity unmask an underlying familial hyperinsulinism syndrome or primary insulin hypersecretion [28], either of which may have also contributed to the development of obesity. In retrospect, some of the patients provide medical history suggestive of familial syndromes. Specific mutation(s) associated with this postbariatric surgical nesidioblastosis syndrome have yet to be identified, however.

While weight gain is associated with islet expansion, weight loss and improved insulin sensitivity would be expected to lead to normalization of increased beta-cell function or mass associated with previous obesity [28]. Thus, it is also possible that failure of regression plays a pathologic role in these patients. In fact, patients achieving weight loss with laparoscopic adjustable gastric banding (LAGB) – a purely restrictive procedure – may experience a transient milder asymptomatic hyperinsulinemic hypoglycemia [29]. To date, however, profound hyperinsulinemic hypoglycemia or islet hyperplasia has not been seen following exclusively restrictive procedures, suggesting that an anatomic or functional consequence of gastric bypass surgery may play an important role. Moreover, the time course of presentation 1–2 years postoperatively, at a time at which weight loss has stabilized, suggests that the process includes stimulation of islet hyperplasia and not solely failure of islet apoptosis.

Finally, it is possible that altered levels of islet regulatory protein(s) following gastric bypass surgery may induce islet hyperplasia. Incretin hormones have been suggested as major candidates to mediate the islet hyperplasia [8**,9**]. Distal intestinal delivery of nutrients postgastrectomy stimulates glucagon-like peptide 1 (GLP-1) or GIP secretion, increasing insulin secretion and contributing to alimentary hypoglycemia [12]. Likewise, GLP-1 levels are increased in patients following Roux-en-Y surgical procedures [30]. This is in contrast to suppression of nutrient-stimulated GLP-1 secretion following weight loss mediated by very low-calorie diet [31]. Furthermore, GLP-1 can also produce islet hyperplasia in rodents [32]. The capacity for adult human islets to expand, however, is lower than that of rodents. Furthermore, high doses of GLP-1 analogues administered over extended periods to rodents or cynomolgus monkeys has not produced similar islet pathology [33]. Similarly, abnormal pancreatic histology has not been reported postgastrectomy in humans to date – a condition also associated with increased GLP-1, suggesting this is not the sole mediator of the syndrome. Thus, the role of GLP-1 in mediating this syndrome remains poorly understood, and multiple hormonal and metabolic changes may be involved in the pathogenesis of postbypass hypoglycemia syndrome.

**Conclusion**

While enhanced insulin secretion postbypass is a component of the dumping syndrome, the severity of hyperglycemia and hyperinsulinemia in some patients suggests a newly recognized pathological syndrome. Potential mechanisms in these patients include: improved insulin sensitivity after weight loss unmasking an underlying familial hyperinsulinemia syndrome; lack of regression of increased beta-cell mass that developed with prior obesity; or active expansion of beta-cell mass mediated by the altered hormonal and metabolic milieu following Roux-en-Y gastric bypass surgery. Given the large number of gastric bypass procedures performed annually, and the relative rarity of postbypass hyperinsulinemic hypoglycemia of severity requiring endocrine evaluation or surgery, it is possible that an underlying hyperinsulinemia syndrome may have preexisted in such patients and potentially contributed to weight gain. We suggest that the preoperative evaluation for gastric bypass surgery should include detailed questioning for symptoms suggesting exercise or meal-related hypoglycemia to potentially identify patients at risk for this complication of obesity surgery.

Further investigation will be critical to understand mechanisms of beta-cell expansion in the adult human. These investigations may be informative, providing new means to treat or prevent type 2 diabetes or to augment islet expansion for human transplantation. At present, given the increasing prevalence of gastric bypass, clinicians may wish to consider that severe hypoglycemia in postbypass patients unresponsive to nutritional modification may indicate an underlying disorder of beta-cell function.
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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 462).


Comprehensive review of the pathophysiology and treatment of the dumping syndrome.


One of two studies describing initial recognized cases of postbariatric surgery hyperinsulinemic hypoglycemia.


One of two studies describing initial recognized cases of postbariatric surgery hyperinsulinemic hypoglycemia.


