Surgical Treatment of Clinically Significant Reactive Hypoglycemia Nesidioblastosis, Post-Gastric Bypass

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Abstract

Introduction: Gastric bypass (GB) used to be a standard surgical procedure performed for weight loss. Delayed complications following GB may outweigh the initial benefits in some patients. As manifested in some patients with clinical symptoms of hypoglycemia, Dumping Syndrome may, over time, progress to persistent Hyper-Insulinemic Hypoglycemia (HIH) and, in some cases, with Nesidioblastosis (NB) [1]. The current recommended surgical treatment includes > 95% pancreatectomy [2] which has been shown to cause irreversible diabetes in 90% of patients. We discuss fifteen patients who underwent gastric bypass revision to duodenal switch with a resolution of hypoglycemic symptoms.

Method: This is a retrospective analysis of prospectively collected data.

Results: Fifteen patients were seen and evaluated for clinically significant symptoms of hypoglycemia after the GB procedure. No insulinoma was discovered. Revision to Duodenal Switch (DS) was performed. Symptoms of HIH were reversed after surgery, and patients have remained 100% symptom-free post-operative follow-up.

Conclusion: In our experience, DS is a preferable operation for the correction of HIH. Duodenal switch shows greater efficacy with significantly fewer complications with tailored alimentary and standard channel lengths and should be considered before near-total pancreatectomy. Near-total pancreatectomy may be the last option for those who do not respond to the GB reversal.

Keywords
Gastric bypass, Duodenal switch, Revision, Hyper-insulinemic hypoglycemia, Nesidioblastosis, Pancreatectomy, Dumping syndrome

Background

Bariatric surgeries are the most effective intervention proven to result in significant and sustained weight loss and improvement or resolution of comorbidities associated with obesity, such as type II diabetes [3,4]. Different types of surgical weight loss procedures have varying degrees of safety and outcome profiles [5,6]. Roux-en-Y gastric bypass (GB) is a type of weight-loss surgical procedure for morbid obesity and its associated comorbidities. In GB, a small 2-3-ounce pouch is created just distal to the gastroesophageal junction and is connected to a Roux-en-Y limb created of the proximal small bowel. The stomach, pyloric valve, duodenum, and a varying segment of the jejunum are bypassed. There is nutritional and physiological sequela attributed to the exclusion of the pyloric valve from the digestive pathway [7]. Dumping syndrome and HIH have been recognized as a long-term complication of GB in a subset of patients [8,9]. In small series, near-total pancreatectomy has been recommended to treat clinically significant hypoglycemia and NB after gastric bypass operation with varying outcome [10].

Duodenal switch procedure was first described in 1987 as a surgical intervention to treat primary bile reflux gastritis or decrease symptoms in post gastrectomy and gastroduodenostomy patients [11]. This procedure was later adapted as a bariatric surgical solution for the treatment of morbid obesity by increasing longitudinal gastrectomy to 75%, reducing gastric capacity and acid production, and extending the Roux limb to induce fat malabsorption resulting in weight loss.
In our experience, HIH can be reversed with GB to (DS) or Sleeve Gastrectomy revision while avoiding the complication of 80% pancreatectomy as described [14].

Pathophysiology of Hypoglycemia in Post-RNY-GB Patients

Nearly 50% of patients who undergo GB will develop dumping syndrome [15-17]. The dumping syndrome phenomenon is a postprandial disorder of rapid emptying of stomach pouch contents into the small bowel characterized by tachycardia, diaphoresis, dizziness, fatigue, and weakness [16,17]. The symptoms of hypoglycemia as a part of dumping syndrome may present early or late [18]. NB may develop in a group of patients with progressively advanced dumping syndrome over time.

HIH (plasma glucose < 50-55 mg/dl) is characterized by neuroglycopenia (inadequate glucose supply of the brain) and inappropriately elevated insulin concentrations [19-21]. Our understanding of this condition has evolved over the years. HIH is thought to result as an acquired phenomenon or from the pancreas' failure to decrease insulin secretion after years. HIH is thought to result as an acquired phenomenon or from the pancreas' failure to decrease insulin secretion after GB surgery adaptively [22]. The pylorus controls the flow of contents of the stomach into the small bowel. With the GB procedure, the duodenum and pyloric valve are entirely excluded. The pyloric valve's exclusion results in bolus entry of food in the small bowel in an unregulated format. Rapid presentation of nutrients into the small intestine allows for superfluous absorption of carbohydrates, especially after a carbohydrate-rich meal, stimulating L cells of the distal ileum. This occurrence of the dumping syndrome is a stimulus of Glucagon-Like Peptide One (GLP-1) release [23]. GLP-1 stimulates regeneration and expansion of pancreatic beta-cells by process of neo-genesis and proliferation [24]. Studies have demonstrated the proliferative and anti-apoptotic properties of GLP-1 in human and rodent beta-cells.

Laboratory studies of rats treated with GLP-1 resulted in two significant findings:

1. An increase in cell proliferation of the endocrine and exocrine pancreas and
2. A reduction of apoptotic cells within the islets and exocrine pancreas [25].

Increased beta-cell mass induces hypoglycemia after GB surgery. The hypoglycemia is due to beta-cell proliferation and overactivity (Nesidioblastosis) as a result of GLP-1 stimulation [26]. Without pyloric regulation, dumping occurs, stimulating GLP-1, increasing proliferation, overactivity of Beta cells, and inhibiting programmed cell death of pancreatic islets, leading to inappropriately increased insulin-secreting cell hypertrophy [24,25]. Postprandial decreased blood glucose levels may present from endogenous hyperinsulinemia from resulting abnormal islets of Langerhans due to Nesidioblastosis observed in patients who have undergone GB as a treatment for severe obesity.

Diagnosis of Hyper-Insulinemic Hypoglycemia

No definitive standardized method for the diagnosis of HIH has been outlined. In addition to hypoglycemia symptoms, confirmation of the disorder ideally requires concomitantly elevated insulin (> 3 µU/ml), a negative oral hypoglycemia agent screen, and elevated C-peptide (> 0.6 ng/ml) [18]. Hypothetically, during spontaneous postprandial episodes of hypoglycemia-related to hyperinsulinemia, C-peptide levels may be obtained due to its half-life (30 minutes). This finding is not a confirmation of excessive beta-cell secretion; instead, it rules out exogenous insulin administration, where levels would be low or undetectable. Provocative testing such as oral glucose tolerance test and mixed meal studies are suggested to induce hypoglycemia and its symptoms [27,28]. In our opinion, symptoms and laboratory studies differentiate the two conditions of Nesidioblastosis and insulinomas significantly that the CT scan may not be of any added value (Table 1). Insulinomas, insulin-secreting tumors of the pancreas, may cause hypoglycemia, but not postprandially. Patients diagnosed with insulinoma have increased insulin production that stimulates hypoglycemia during fasting. Hallmark symptoms of insulinoma are tachycardia, dizziness, and diaphoresis when patients do not feed frequently. On the contrary, HIH induced after GB surgery presents with hypoglycemic symptoms after feeding. Fasting ameliorates patients' hypoglycemic symptoms [9]. This correlates directly with inappropriate insulin secretion from hypertrophied beta-cells due to GLP-1 stimulation as a result of the rapid emptying of gastric contents into the small bowel with increased carbohydrate absorption after feeding.

Current Recommendations of Treatment

HIH and Nesidioblastosis have been reported to resolve over time in some patients and neuroglycopenia may not be evident [24]. Majority of patients suffering from HIH respond to dietary modification, such as eating frequent, small, low-carbohydrate, high protein meals. Medications to decrease the absorption rate of carbohydrates and hormone antagonists such as Acarbose and somatostatin respectively have been empirically associated with symptom modification in select patients as an aid to nutritional changes. Patient compliance and its associated cost are significant factors for their limited use. Carbohydrate inhibitors (such as Acarbose) in patients with dumping syndrome and HIH who do not follow dietary guidelines is contraindicated as it can create significant gastrointestinal adverse effects [2]. For those patients with

| Table 1: Fasting vs. Postprandial Parameters of Insulinoma vs. Nesidioblastosis [23]. |
|---------------------------------------------------------------|
| Fasting Insulin | Postprandial Insulin | Fasting Glucose 60-110 mg/dl | 1 hour post prandial Glucose |
| weekdays | evenings | |
| Insulinoma | ⬤ | ⬤ | ⬤ | ⬤ ⬤ |
| Nesidioblastosis | ⬤ ⬤ ⬤ | ⬤ | ⬤ | ⬤ ⬤ |

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HIH severe enough not-responding to nutritional intervention or medication, surgery has been advocated. The surgical procedure recommended has been 80-95% distal pancreatectomy [2]. This procedure reduces the amount of inappropriately secreted insulin, reducing hypoglycemia episodes by removing the cells that produce and release the insulin - Beta cells. Retrospectively, near-total pancreatectomy has been shown to cause hyperglycemia as a complication [29]. Since gastric feeding reverses the hypoglycemia after gastric bypass, a non-pancreatic etiology is possible. As an irreversible surgical operation, distal pancreatectomy, patients who are affected are no longer able to produce adequate insulin, leading to hyperglycemia and the associated complications. It has been shown that resections greater than 90% frequently result in insulin dependency and irreversible diabetes [14].

Materials and Methods

This is a retrospective study of prospectively gathered data. Fifteen patients presented with dumping and postprandial hypoglycemia symptoms as their primary and significant chief complaints that were affecting their quality of life. Patients were assessed and carefully considered for revision surgery. All fifteen patients underwent revision from GB to DS. The duodenal switch was performed with a length of the alimentary and common channels measured as a percentage of the small bowel's measured total length. Common and Alimentary channels were measured to 10% and 40% of the total small bowel length, respectively [13].

Results

A total of 15 patients were identified for this study. These include patients seen in our clinic for revision of failed GB, with a primary complaint of clinically significant dumping, hypoglycemia unresponsive to conservative treatment, including behaviors and dietary changes; the eligibility requirement was symptoms consistent with hypoglycemia following GB. Of these patients, 12 were females, and 3 were males; the mean age was 42.53 years with a standard deviation of 7.07. The mean weight and BMI at which these patients had their DS was 287.93 lbs. and 49.63 respectively; the mean weight and BMI before surgery for revision to DS was 223.13 lbs. and 37.92 respectively, and two years after DS was 158.4 lbs. and 27.52 with a mean reduction of the total weight of 64.73 lbs. and 10.4 of BMI.

Abdominal Ultrasound and CT scan or both had been used as a diagnostic study in all patients to rule out insulinoma. The weight loss peak occurred at 16 months at 115 lbs (58-173). All of these patients had reported dumping syndrome, which did not respond to conservative treatment. In all cases, their symptoms worsened over time, with significant psycho-social complications impacting the regular and routine function of their everyday life. Patients underwent physical examinations and routine laboratory tests. The patients were evaluated by a complete medical history and physical exam. Their records, which included comprehensive metabolic workup and radiologic studies, were reviewed. None of these patients presented with fasting hypoglycemia. All patients had normal fasting blood glucose levels with significant symptomatic postprandial hypoglycemia diagnostic of Nesidioblastosis.

There was no radiologic evidence of insulinoma. They all had imaging studies, including CT scans and US. Six of the fifteen patients (all females) had a temporary gastrostomy tube inserted to improve their nutritional status before revision the GB to the DS operation. Their symptoms were absent with the feedings via the gastrostomy tube and present with oral intake. Placing a feeding tube in the remnant stomach allowed incorporating the previously omitted pyloric valve and regulated nutrient presentation to the small intestine.

Duodenal switch procedure, as mentioned previously, returns a function of the remnant stomach, pyloric valve, and duodenum and lengthening of the alimentary limb. By reinstating pyloric valve function, control of nutritional content entering into the small intestine ameliorated dumping syndrome, HIH and NB.

Patients following DS had complete resolution of HIH symptoms that were interfering with their quality of life. At the time of following, on average three years post-op, they all continue to be free of dumping syndrome symptoms and HIH. DS has shown to carry no secondary risk of pancreatic dysfunction and production of insulin-dependent diabetes, as seen in 90% of patients who undergo pancreatectomy for treatment of the same presenting symptoms.

Discussion

Postprandial hypoglycemia, HIH, is a complication seen in a subset of patients following GB surgery. It is an insidious complication that does not present immediately after surgery but evolves in patients who have progressively worsening dumping syndrome. This is suspected to be caused by GLP-1 stimulation and beta-cell hypertrophy. These patients may present with a broad spectrum of clinical findings, commonly with neuroglycopenia, diaphoresis, significant nausea, and weakness. Our experience indicates that the revision of gastric bypass to the duodenal switch resolves the HIH condition. Restoring normal pyloric function reverses dumping syndrome complications, eliminating postprandial hypoglycemia, and resolves the symptoms of Nesidioblastosis. Unlike near-total pancreatectomy, the duodenal switch procedure does not cause insulin insufficiency and reversed 100% of our patients' symptoms.

Conclusion

Continuous follow-up and observation of these fifteen patients have shown complete resolution of initial post-GB complications. Patients have reported a significant improvement in the quality of life. Risk versus benefit analysis in treating patients with reactive hypoglycemia and Nesidioblastosis with DS operation has shown more significant benefit than risk. In our opinion, the duodenal switch operation is a safer procedure to perform than a near-total pancreatectomy. It should be considered as the treatment of choice for a patient suffering the complication of reactive hypoglycemia and Nesidioblastosis following a gastric bypass operation.

Financial Disclosure

None.
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