Commentary

MOLECULAR METABOLISM

Can reversal of RYGB also reverse hypoglycemia?

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An increasing number of patients affected by excess weight have turned to bariatric surgery for not only weight loss but also for improved metabolic health. This perspective is supported by recent data from controlled clinical trials highlighting the efficacy of bariatric surgery to resolve or improve obesity-related comorbidities including type 2 diabetes, hypertension, and dyslipidemia. However, long-term nutritional and metabolic complications require meticulous attention. One of the most challenging complications is post-bariatric hypoglycemia (PBH), a syndrome typically detected >1 year after surgery. In PBH, fasting glucose levels are normal, but shortly after eating, plasma glucose levels rapidly "spike", with subsequent rapid declines in glucose, sometimes to hypoglycemic levels, within 1–3 h. The underlying pathophysiology of this condition is complex, and includes rapid gastric emptying, excessive postprandial secretion of incretin hormones such as GLP-1, increased insulin secretion, and reductions in counter regulatory hormone responses [1]. Remarkably, these and other changes in systemic metabolism ultimately result from surgically-induced alterations in gut anatomy and nutrient flow (Figure 1). Since current treatment approaches for PBH are not uniformly successful, Davis and colleagues now present results of a prospective case series of 6 patients in whom surgery was performed to reverse RYGB anatomy in order to treat severe PBH [2].

As a first step to determine whether reversal of anatomy would normalize meal-related hormonal and glycemic responses, a gastrostomy (G)-tube was placed in the excluded stomach, and a liquid mixed meal was administered via the G-tube. With this approach, nutrients would exit the remnant stomach via the pylorus and traverse the biliopancreatic limb, mixing with biliary and pancreatic secretions, yielding relative normalization of nutrient flow. Indeed, a prior report demonstrated that chronic G-tube feeding could be a successful treatment for PBH [3]. In the current study, participants having improvements in glucose profiles and no hypoglycemia with the test meal (delivered via the G-tube) were offered surgery, with 4 patients undergoing conversion to sleeve gastrectomy and 2 patients undergoing reversal to near-normal anatomy. Patients were followed for a mean of 20 ± 15 months after revisional surgery. All reported improvement in severity of symptomatic hypoglycemia, with reduction in episodes from 19 to 2 per week. Moreover, post-meal glucose, insulin, and GLP-1 excursions were significantly diminished with both G-tube feeding and after reversal surgery. Not surprisingly, modest weight regain was observed, averaging 5 BMI units, but weight remained substantially lower than pre-RYGB levels. Hormonal, metabolic, and weight profiles did not differ when comparing those with reversal to sleeve gastrectomy vs. reversal to normal anatomy.

Strengths of the current study are its paired design, with patients acting as their own controls, and detailed hormonal analysis. However, small sample size, variable surgical approaches, relatively short follow up, and incomplete cohort data are significant limiting factors. While this study reports 100% success in improving hypoglycemia, previous reports of even smaller series have noted variable responses. For example, two patients with severe PBH had no improvement after reversal [4]. Two additional case reports totaling six patients [5,6] highlight the importance of a successful G-tube trial, while reversal was successful even without a G-tube trial in 9 patients [7]. Nevertheless, selection bias could contribute to findings of benefit in the current study, as the patients who underwent revisional surgery all had successful G-tube meal trials. Information on the screening of potential candidates, with focus on the percentage of patients who did or did not have improved patterns with G-tube feeding, would be helpful to understand the overall success of revisional surgery.

Variation in surgical techniques for RYGB and its revision to sleeve gastrectomy or near-normal anatomy may also contribute to variable responses. For example, does reversal include resection of the roux limb, implicated as a potential contributor to incretin secretion and postprandial intestinal glucose uptake [8]? The technique utilized in the current report was similar to another report [6] but differed from others [4,5,7]. Despite these variables, 10 of the 12 patients in published reports showed improvement in hypoglycemia.

Differential effects on gastric emptying could also impact response to revisional surgery. In our experience, patients often experience symptoms of delayed gastric emptying, such as persistent nausea and vomiting, after revisional surgery. Slowed emptying may contribute to improvements in glycemia but may sometimes require additional surgical procedures for symptom relief. Other factors which may contribute to variable responses include gut microbiota, bile acids, dietary composition, intestinal adaptive responses, and changes in blood flow and innervation (which may not be fully reversible). Finally, inter-individual differences in glucose metabolism and insulin secretion, present prior to original RYGB, may contribute to PBH, and these may remain despite revision in a subset of patients.

Should we recommend reversal of RYGB for patients with severe PBH? The current study supports the hypothesis that altered nutrient flow

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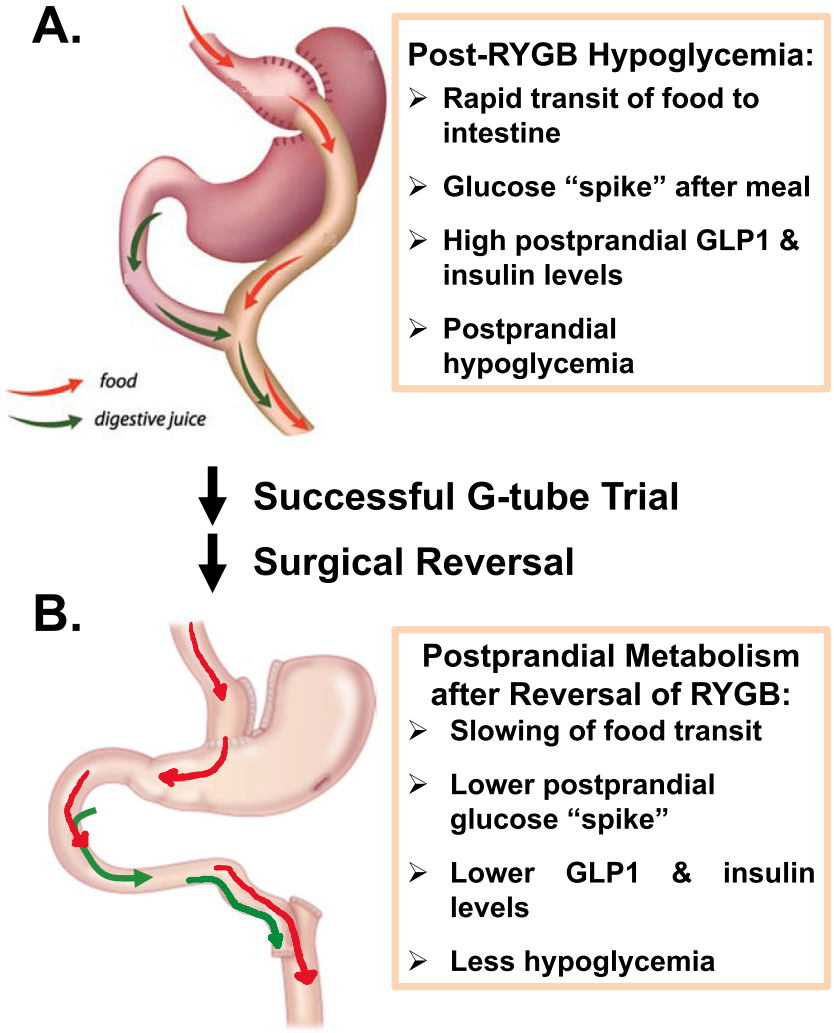

Figure 1: Schematic of differences in glucose and hormonal patterns in patients with (A) hypoglycemia after RYGB surgery and (B) after RYGB reversal surgery.

contributes to disordered glycemia after RYGB and provides some optimism that normalization of nutrient flow by either chronic G-tube feeding [3] or conversion to sleeve gastrectomy or nearly-normal anatomy, when possible, could be effective for some patients. However, given the reported variability in response and small cohorts to date, additional studies addressing the long-term efficacy, and factors associated with beneficial responses, will be required before revisional surgery can be universally recommended. Moreover, it will be important to define whether G-tube meal responses can be used to predict success, and to identify the duration of G-tube feeding required to achieve optimal predictive value, as restoration of nutrient flow may continue to modulate intestinal remodeling and hormonal responses with time [5]. In the interim, we recommend medical nutrition therapy to limit intake of simple carbohydrates, use of disaccharidase inhibitors such as acarbose, and medications to limit incretin and insulin secretion when needed [9]. Although initial reports indicated benefit of partial pancreatectomy, subsequent studies showed incomplete efficacy over time [10]. Adjunctive measures, such as real-time continuous glucose monitoring with predictive alarms which permit self-treatment before neuroglycopenia develops, may improve safety. More importantly, a full understanding of the underlying pathophysiology of PBH is required to allow clinicians to identify patients at highest risk for developing PBH during preoperative assessment, and thus prevent this serious complication.

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