
Alterations in Gastrointestinal Physiology after Roux-En-Y Gastric Bypass

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Morbid obesity is increasing exponentially in the US. Approximately 33.3% of Americans were obese in 1991, versus 25.4% in 1976.^{1,2} Currently, 54.5% of Americans are overweight, with a body mass index > 25.³ Diet and exercise are implemented initially, they usually fail after 2 years. In response to this epidemic, surgical therapies for morbid obesity have evolved. There are several different weight loss operations available, including Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion, duodenal switch, vertical banded gastroplasty, and the LapBand. The most common procedure performed in the US is RYGB, which is both a restrictive and malabsorptive operation. Although there are several variations available for RYGB, the general principles are similar. The first part of the operation creates a gastric pouch of approximately 20 cm³ to restrict oral intake. The second component of the operation involves construction of a biliopancreatic limb that diverts bile and pancreatic fluid from the proximal to the distal small intestine. This distal diversion creates a segment of small bowel that allows food to pass without interacting with bile or pancreatic fluid. This diversion delays the interaction of pancreatic enzymes and biliary secretions with the food bolus. Finally, this bypass effectively alters normal nutrient exposure to the duodenum.

Although this procedure can alter normal physiology, it has the propensity to increase survival for morbidly obese patients. A recent study by Patterson and colleagues⁴ suggests that life expectancy improves by almost 11% after laparoscopic RYGB, compared with diet and exercise alone. Flum and Dellinger⁵ found that morbidly obese patients had a 33% decreased hazard of death after gastric bypass.

Although the Roux-en-Y procedure is an effective therapy for weight loss, it alters normal digestion and nutrient absorption. These alterations can be mild with no apparent sequelae or cause life-threatening complications. After RYGB, severe malnutrition occurs in approximately 4.7% of the patients postoperatively.⁶ The most common nutritional deficiencies in these patients are iron and vitamin B12.⁷ There are numerous case reports that document malnutrition that lead to myopathy and even Wernicke's syndrome.⁸⁻¹¹

To understand the pathophysiologic mechanisms of RYGB, a review of normal nutrient absorption is required. My colleagues and I describe normal nutrient absorption followed by the malabsorptive physiology associated with RYGB.

NORMAL NUTRIENT ABSORPTION

Nutrients are divided into five groups: protein, carbohydrate, fat, vitamins, and minerals. Normal homeostasis and weight maintenance depends on the digestion and absorption of each of these nutrients. Conversely, altered pathways of absorption result in weight loss and potentially substantial deficiencies with devastating consequences.

Protein absorption

Amino acids are the basic components of protein. A chain of 2 or more amino acids is called a peptide. The amino acids in a peptide are linked by the carboxyl group of one amino acid to the amino group of another. A protein is composed of one or more long peptide chains. Smaller proteins, chains of less than 30 amino acids, are referred to as oligopeptides and include somatostatin and vasopressin.

Where the peptide-laden food bolus enters the mouth, cephalic stimulation through acetylcholine enhances acid production from gastric parietal cells. The acid, along with acetylcholine, stimulates pepsinogen release from chief cells. The gastric acid then facilitates conversion of pepsinogen into pepsin. Cleavage of pep-

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sinogen into pepsin requires a gastric pH ≤ 5 . Pepsin then initiates the cleavage of protein into peptides. The stomach absorbs very few peptides or amino acids. When the peptides and amino acids enter the duodenum, the duodenal and jejunal epithelial cells release cholecystokinin (CCK).¹² Presence of food in the antrum, antral distention, and vagal stimulation increase the production of gastrin. Gastrin stimulates CCK also.¹³ CCK stimulates release of trypsinogen from pancreatic acinar cells. Trypsinogen is released into the duodenum and cleaved into its active form, trypsin, by enterokinase, an enzyme released from the duodenal mucosal cells. Trypsin activates chymotrypsin and procarboxypeptidases A and B. Chymotrypsin and the procarboxypeptidases are produced from the pancreatic acinar cells as well. All of these pancreatic enzymes hydrolyze proteins into amino acids or oligopeptides. Trypsin and chymotrypsin are endopeptidases that cleave internal peptide bonds while procarboxypeptidases cleave the carboxy terminals of the peptide chains.

In the duodenum, brush-border peptidases digest oligopeptides that are absorbed through the sodium-dependent amino acid cotransporters located along the luminal border of the enterocyte. Although 50% of protein absorption occurs in the duodenum, the entire small bowel is capable of protein absorption. By midjejunum, the overwhelming majority of protein absorption is completed.

Carbohydrate absorption

Monosaccharides, including glucose, fructose, and galactose, are the most basic forms of carbohydrates. Dietary carbohydrates exist as disaccharides, such as sucrose, maltose, or lactose or as polysaccharides such as starch. Initially, salivary and pancreatic amylase hydrolyze polysaccharides into oligosaccharides, such as disaccharides and trisaccharides. These oligosaccharides are additionally broken down into monosaccharides by oligosaccharidases in the brush border of the intestinal mucosa.¹⁴ For example, the intestinal enzyme sucrase digests sucrose into the monosaccharides glucose and fructose. Maltase divides maltose into two glucose molecules and lactase digests lactose into the monosaccharides glucose and galactose. Glucose and galactose are transported into the cell by active transport using a Na⁺-K⁺ ATPase pump. Fructose is transported passively through carrier-facilitated diffusion. Carbohy-

drate absorption starts in the duodenum and is completed usually by the first 100 cm of small intestine.

Lipid absorption

Lipids are the largest energy source in the body and 93% of dietary lipids are absorbed in the proximal two-thirds of jejunum.¹² Dietary lipids include free fatty acids, triglycerides, phospholipids, and cholesterol. When lipids enter the duodenum, the I and S cells, located within the duodenal mucosa, secrete CCK and secretin, respectively. CCK and secretin stimulate gallbladder contraction and pancreatic secretion. The pancreas secretes the lipolytic enzymes lipase, cholesterol esterase, and phospholipase A2. These enzymes digest distinct lipid components. Lipase hydrolyzes triglyceride molecules into a monoglyceride and two fatty acids. Phospholipase A2 hydrolyzes phospholipids into a fatty acid, a phosphoric acid, and a nitrogenous base. Cholesterol esterase cleaves cholesterol esters into free cholesterol. After fat digestion by these distinct enzymes, bile-salt–formed micelles emulsify the lipid byproducts. The strongly polar bile acids align their hydrophilic tails externally and their nonionized, hydrophobic heads internally to form a micelle. This emulsification process provides a nonpolar environment to harbor and transport lipid byproducts into the aqueous blood. Ultimately, enterocytes absorb the micelles. Once absorbed into the enterocyte, the triglycerides and cholesterol are resynthesized. These compounds combine with other nonpolar lipids, phospholipids, and proteins to form lipoproteins called chylomicrons. Chylomicrons are transported from the enterocyte into the lymphatic system and eventually into the thoracic duct that enters the bloodstream through the left subclavian vein. Fat absorption, including fat soluble vitamins, occurs throughout the entire small bowel although excess bile salts are absorbed in the terminal ileum.¹⁵

Bariatric procedures

Surgical therapy for morbid obesity occurs through either restricting food intake or decreasing absorption from the intestinal tract. Several techniques reduce the size of the stomach to induce early satiety and limit oral intake. These techniques include gastric banding or stapling. Malabsorptive operations decrease the amount of bowel available for absorption and divert bile and pancreatic enzymes from the proximal to the distal bowel. These two alterations limit food digestion and produce

malabsorption. There are several surgical options available to construct this restrictive or malabsorptive state.

MALABSORPTION FROM RYGB

Protein

In addition to a decreased dietary intake of proteins secondary to the gastric pouch, the RYGB induces protein malabsorption. Under physiologic conditions, the majority of protein is absorbed in the duodenum. After RYGB, protein never enters the duodenum. Protein absorption is limited to the distal jejunum and ileum.

Other components of the RYGB contribute to protein malabsorption. Pepsinogen, as discussed already cleaves protein into peptides. After RYGB, Sundbom and colleagues¹⁶ found a substantial decrease in pepsinogen levels from the gastric remnant. Decreased levels of pepsinogen are secondary to the vagotomy that occurs with gastric partitioning. Vagotomy negates cephalic stimulation and decreases acid secretion and ultimately decreases pepsinogen levels. Without pepsinogen, many protein molecules are left intact and are not absorbed. Even if the gastric remnant releases a basal level of pepsinogen into the duodenum, pepsinogen does not interact with the ingested protein until it traverses the jejunojejunostomy. This delays protein cleavage and small bowel absorption.

Along with the restrictive component and decreased pepsinogen levels, decreased production of pancreatic enzymes contributes to protein malabsorption. In 1971, Ito and Mason¹⁷ demonstrated a 40% reduction in pancreatic enzyme secretion after a gastric bypass. They concluded that this finding resulted from decreased gastrin levels.¹⁷ Discussed here already, food in the antrum, antral distention, and vagal stimulation induce gastrin secretion. Gastrin then stimulates the release of CCK. Without food in the excluded antrum, antral distention and vagal stimulation of G cells do not occur. Interestingly, Ito and Mason¹⁷ showed increased pancreatic secretion after restoration of gastric continuity; diminishing the role of vagotomy on pancreatic secretion. Under physiologic conditions, as peptides pass through the duodenum, the duodenum releases CCK and causes the pancreas to secrete proteolytic enzymes. Theoretically, because the peptides never traverse the duodenum, this physiologic process is omitted as well. Several studies do not show any changes in CCK levels after RYGB.^{18,19}

Unlike fat or carbohydrate, protein is not stored. All protein in the body has some biologic function. Because

proteins function as enzymes and provide structural support to the body, protein deficiency has serious consequences, including poor wound healing, decreased immune function, muscle weakness, weight loss, mental apathy, anemia, pressure sores, depigmented hair or skin, and diarrhea. The most severe form of protein deficiency is referred to as kwashiorkor. Currently, little data exists about protein levels after RYGB. Protein deficiency was documented in 4.7% of patients after RYGB by Faintuch and colleagues.⁶ Although this percentage is low, the real percentage of protein deficiency is difficult to document because of the lack of data.

Carbohydrate

Similar to protein, RYGB alters carbohydrate digestion and absorption. Under physiologic conditions, most carbohydrate absorption occurs within the first 100 cm of small intestine after interacting with pancreatic amylase. Because ingested carbohydrates bypass the duodenum, pancreatic amylase stimulation and release is reduced. After passing from the gastric pouch, carbohydrates travel through the Roux limb as intact polysaccharides. After passing the jejunojejunostomy, the polysaccharides interact with a small amount of basal amylase that is secreted from the pancreas through the biliopancreatic limb. The limited pancreatic amylase hydrolyzes the polysaccharides into oligosaccharides and allows minimal carbohydrate absorption in the remaining small intestine. The combination of decreased absorptive surface area, decreased pancreatic amylase secretion, and delayed interaction of amylase with the polysaccharides limits carbohydrate absorption.

Carbohydrates are a major source of energy for body metabolism and the sole energy source for the brain and red blood cells. The liver and skeletal muscle store carbohydrates as glycogen. In the absence of adequate carbohydrate substrate, fat and protein are broken down through gluconeogenesis into carbohydrates to provide a nutritional substrate for the brain and red blood cells. A deficiency in carbohydrates can lead to a deficiency in protein.

The anatomic alterations created during the RYGB probably contribute to dumping syndrome. The early phase of dumping occurs immediately after eating and is characterized by abdominal cramping, nausea, vomiting, diarrhea, dizziness, palpitations, and diaphoresis. Increased gastric emptying after RYGB leads to rapid filling of the small bowel with hyperosmolar chyme.

This causes an osmotic shift of extracellular fluid into the bowel to restore isotonicity. Also, this shift causes intestinal distention, abdominal cramping, nausea, vomiting, and diarrhea. Bowel distention causes the release of vasoactive intestinal peptide and serotonin. These two hormones are associated with diaphoresis, dizziness, and palpitations. Fluid shifts from the intravascular space can accentuate the vasomotor symptoms. Early phase symptoms are accentuated by a surge in blood glucose levels.^{20,21}

The late phase occurs 1 to 4 hours after eating and is characterized by sweating, dizziness, and fatigue. A delayed surge in insulin secretion with rebound hypoglycemia causes this phase. The primary treatment for dumping syndrome includes a decrease in simple carbohydrate intake. This can be a problem in patients with a carbohydrate deficiency. Symptom improvement can occur by modifying the diet to small, frequent meals that are high in fiber, protein, and complex carbohydrates with minimal simple sugars.²¹ Dumping syndrome occurs to some degree in approximately 70% to 75.9% of patients after bariatric surgery.²²⁻²⁴ Although this percentage seems high, the overwhelming majority of patients only experience transient dumping as they modify their diets over time.

Lipid

Under physiologic conditions, fat passes into the duodenum and stimulates CCK. In turn, CCK stimulates the gallbladder and pancreas to release bile and lipolytic enzymes. After RYGB, the secretion of bile and lipolytic enzymes is reduced because lipids never pass through the duodenum. Lipids, including triglycerides, phospholipids, and cholesterol, travel through the Roux conduit as intact structures until they reach the jejunojejunostomy. Delayed breakdown of dietary fats and the delayed formation of micelles limit the amount of fat available for absorption. Undigested fat passes into the colon producing fat malabsorption and steatorrhea.

Vitamins and minerals

RYGB reconstruction can cause deficiencies in certain vitamins and minerals. Iron, calcium, and thiamine (vitamin B1) are absorbed primarily in the duodenum. After RYGB, these vitamins never enter the duodenum and their absorption is decreased considerably. Because vitamin D is a fat-soluble vitamin, it is poorly absorbed after the RYGB. Ultimately, this leads to an additional

decrease in serum calcium. Many patients experience progressive bone loss over time. Vitamin D deficiency is more likely to occur after a biliopancreatic diversion than RYGB because a greater degree of fat malabsorption. Deficiencies of vitamin D and calcium after both types of malabsorptive procedures can increase bone turnover and decrease bone mass.²⁵⁻²⁷ It is imperative to monitor hemoglobin, calcium, and thiamine levels regularly.²⁸

In addition to vitamin D, any of the fat-soluble vitamins can become deficient after RYGB. This includes vitamins A, E, and K. There are reports of ocular deficiency after biliopancreatic diversions as a result of vitamin A deficiency.^{29,30} There is no such data after RYGB. Vitamin K deficiency can lead to a decrease in vitamin K-dependent clotting factors. Coagulation studies should be monitored closely for patients taking warfarin.³¹

Cobalamin (vitamin B12) is absorbed in the terminal ileum. In order for absorption to occur, cobalamin must be linked to the glycoprotein, intrinsic factor. Intrinsic factor is produced by parietal cells in the stomach and released after hormonal stimulation from acetylcholine, histamine, and gastrin. Pepsin and hydrochloric acid are needed to separate B12 from the protein bolus in the stomach. Without hydrochloric acid in the proximal pouch, RYGB patients cannot cleave B12 from the protein moiety. The excluded stomach and bypassed duodenum prohibit binding of free B12 to intrinsic factor. Several investigators showed that bound B12 is not absorbed as well as administered crystalline B12 orally after a RYGB or partial gastrectomy.³²⁻³⁴ Smith and colleagues³⁵ found that B12 was not digested and essentially malabsorbed. They recommended supplementing with either monthly parenteral B12 or daily oral crystalline preparations. Meanwhile, a normal Shilling test can occur after RYGB. This finding suggests that the bypassed stomach continues to secrete some degree of intrinsic factor^{36,37} and that B12 deficiency results from malabsorption; not a decrease in intrinsic factor.

Restrictive procedures, such as gastric banding and gastroplasty, can cause vitamin and mineral deficiencies as well.³⁸⁻⁴⁰ There are several reports of vitamin A, C, D, E, K, B1, B2, and B6 deficiencies. Many of these findings were present in patients taking regular multivitamin supplements. MacLean and colleagues⁴¹ reviewed 17 patients admitted for either malnutrition or excessively rapid weight loss after a horizontal gastroplasty. They

found substantially decreased levels of serum thiamine and folate compared with preoperative levels. Thiamine and folate levels were low in 50% and 65% of these patients, respectively. These values can have far-reaching indications as more patients undergo the LapBand procedure.

Prevention and control of deficiencies

RYGB decreases the quantity of food patients consume. Daily oral supplementation with a chewable multivitamin, as a result, is recommended. Although there is little published data about treatment regimens for micronutrient deficiencies after RYGB, low serum levels of iron, B12, and folate require either a multivitamin or specific supplementation of the deficient micronutrient. A minimum daily dose of 350 ug of oral B12 is sufficient to maintain normal serum levels after a RYGB⁴² and 500 ug of oral B12 is sufficient to correct the majority of deficiencies. Intramuscular injections can be used as well. This regimen entails an injection of 1,000 ug followed every 2 to 4 weeks with 100 to 500 ug to maintain normal serum levels. Nasal sprays and gels can also provide effective prophylaxis. Meanwhile, low folate levels are corrected with multivitamin supplementation, which typically contains 400 ug of folate.^{43,44}

A complete blood count and serum levels of iron, total iron-binding capacity, and vitamin B12 should be obtained in patients preoperatively and again postoperatively at 6-month intervals during the first 2 years. These levels should be checked annually thereafter.⁴⁵ Although most surgeons do not measure serum calcium nor provide supplements,⁴⁶ calcium supplementation is relatively harmless. In addition to a multivitamin, 1,200 mg of calcium should be taken daily.⁴⁷

Multivitamins and oral iron supplements do not consistently correct low serum iron levels.^{48,49} Yet, only 50% of low Hgb levels are associated with iron deficiency. Many patients with severe iron deficiency anemia (Hgb < 10 g) respond rarely to oral iron supplementation alone. Patients do respond to a variety of therapeutic measures including IM iron injections, IV iron dextran, SC injections of erythropoietin and blood transfusions. Total abdominal hysterectomy might be required in some patients with menorrhagia. Prophylactic oral supplements containing 650 mg of elemental iron in premenopausal women after RYGB are recommended.⁴⁷

Adequate protein and calorie consumption is necessary to maintain muscle mass. Patients unable to con-

sume adequate amounts of protein and calories can feel weak and develop nutritional deficiencies. Caloric intake should be between 1,000 and 1,500 cal/kg and patients with an initial body mass index of < 50 kg/m² should consume 60 to 70 g of protein per day. Patients with a body mass index 50 to 70 kg/m² can need up to 100 g of protein per day.⁵⁰

Other recommendations

Ursodiol, which increases the solubility of bile salts, reduces the risk of developing gallstones to approximately 2% if taken at 300 mg four times a day. Without ursodiol, gallstones can occur in 30% of patients with considerable weight loss from either medical or surgical methods.^{51,52} Ursodiol is given as long as the patient continues to lose considerable weight (> 3% of body weight per month) or for the first 6 months after an operation. Cost and the rather large size of the pill limit its use by patients.⁵³

Physical activity is recommended postoperatively. A strenuous activity program on a very low calorie diet causes an excessive loss of lean body mass and an undesirable effect. A knowledgeable physical therapist or exercise physiologist should guide any activity greater than walking in the early postoperative period.⁵⁴

Meanwhile, adequate fluid intake prevents constipation, hypotension, urinary tract infections, kidney stones, and hyperuricemia. Patients should sip small quantities of liquid on a regular basis to avoid these problems. They should avoid excessive sweating to limit volume depletion in the early postoperative period. In addition, most patients should discontinue diuretics postoperatively as some degree of volume depletion develops.⁵³

The demand for bariatric surgery increases as the epidemic of morbid obesity continues to worsen. In 1990, surgeons performed approximately 4,900 bariatric procedures compared with 100,000 procedures in 2000. Clearly bariatric surgery achieves a sustained weight loss with long-term followup^{4,23,55-57} and resolves associated comorbidities including diabetes and hypertension.⁵⁸⁻⁶⁵ The principles that induce weight loss can result in deficiencies of protein, fat, carbohydrate, vitamins, and minerals. Understanding the physiologic basis of weight loss is crucial to produce weight loss without causing malnutrition. Because the number of RYGB continues to increase, more research is needed to define the physiologic mechanisms associated with this procedure.

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