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Gastric Acid Secretion and Vitamin B_{12} Absorption After Vertical Roux-en-Y Gastric Bypass for Morbid Obesity

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Objective

This study sought to determine the basal and peak-stimulated acid secretion from the proximal gastric pouch and its relationship to absorption of free and food-bound vitamin B_{12} after gastric bypass for morbid obesity.

Summary Background Data

Gastric bypass can be performed safely and provides acceptable weight loss, but concerns remain about possible long-term complications such as vitamin B_{12} malabsorption. The authors hypothesized that by constructing a small pouch of gastric cardia, acid secretion into the pouch would be low, leading to maldigestion of food-bound vitamin B_{12} with subsequent malabsorption.

Methods

Basal and pentagastrin-stimulated peak acid outputs from the proximal gastric pouch were measured in ten patients after vertical Roux-en-Y gastric bypass using a perfused orogastric tube technique. Absorption of free and food-bound ^{57}Co-vitamin B_{12} was evaluated separately using 24-hour urinary excretion.

Results

Basal (mEq/hr, $\bar{x} \pm$ standard error of the mean [SEM]) and peak-stimulated (mEq/30 min) acid secretions from the proximal gastric pouch were markedly decreased compared to those for age- and sex-matched hospital control subjects (0.01 ± 0.01 *vs.* 4.97 ± 0.66 and 0.08 ± 0.04 *vs.* 12.11 ± 1.34, respectively; $p < 0.001$ for each). While absorption of free vitamin B_{12} was not statistically different from that of control subjects (11 ± 2 *vs.* $15 \pm 2\%$; $p > 0.05$), absorption of food-bound vitamin B_{12} was decreased (0.8 ± 0.2 *vs.* $3.7 \pm 0.5\%$; $p < 0.01$).

Conclusions

After vertical Roux-en-Y gastric bypass for morbid obesity, acid secretion is virtually absent and food-bound vitamin B_{12} is maldigested and subsequently malabsorbed. The results of this study suggest that postoperative vitamin B_{12} supplementation is important and can be achieved with either monthly parenteral vitamin B_{12} or daily oral crystalline preparations.

Morbid obesity, defined as weight greater than 100% or 100 pounds above ideal body weight, is currently a serious national health concern affecting nearly 3.8 million men and 4.5 million women throughout the United States.[1] These individuals are at increased risk for weight-related, co-morbid medical conditions.[2] Because of the poor long-term success of dietary and medical treatments, a variety of surgical approaches to induce and maintain a satisfactory weight loss have been developed.[3] In terms of weight loss, gastric bypass has been a "gold standard" against which other operations are compared, with most patients losing 50% to 75% of their excess body weight.[4-9] However, gastric bypass has not been widely accepted as the surgical treatment of choice for patients with morbid obesity owing in part to concerns about the long-term physiologic and nutritional consequences of the anatomic bypass of the stomach and duodenum (Fig. 1). Notable among these complications are stomal ulcers at the gastrojejunostomy and vitamin B_{12} deficiency. These complications remain poorly understood.

Our aim was to determine basal and peak-stimulated gastric acid secretion from the proximal gastric pouch and its relationship to absorption of free and food-bound vitamin B_{12} after gastric bypass for morbid obesity. We hypothesized that by constructing a small pouch of gastric cardia (< 10 mL), acid secretion into this pouch would be very low. The resultant decreased acid secretion would fail to liberate vitamin B_{12} from the foods containing it (maldigestion) and would lead to malabsorption of ingested vitamin B_{12}.

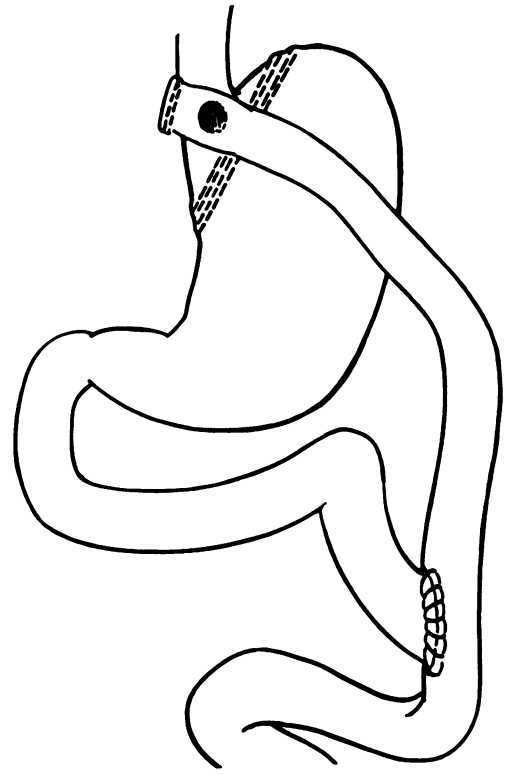

Figure 1. Vertical Roux-en-Y gastric bypass. The stomach is stapled across completely just distal to the cardia thereby preventing orally ingested food from reaching the remainder of the stomach. A side-side gastrojejunostomy is created between the proximal gastric pouch and a 50-cm Roux-en-Y limb of the proximal jejunum. (Published with permission from the Mayo Foundation.)

METHODS

Study Group

Ten subjects (three men and seven women) with a mean age of 40 years (range, 29 to 54 years) were studied at a mean of 17 months (range, 3 to 38 months) after vertical Roux-en-Y gastric bypass (Fig. 1) for the treatment of medically complicated morbid obesity. These subjects had lost a mean ± standard error of the mean (SEM) of 99 ± 10 pounds since the operation. They were chosen randomly from a cohort of 32 patients who had undergone Roux-en-Y gastric bypass in the previous 36 months at our institution. Fifteen healthy volunteers (9 men and 6 women) with a similar mean age of 35 years (range, 22 to 56 years) were enrolled as normal control subjects for the vitamin B_{12} absorption studies. This study was approved by the Institutional Review Board of the Mayo Clinic, and informed consent was obtained from all subjects. Premenopausal women had to have negative findings on a serum pregnancy test before inclusion. Subjects were screened carefully to ensure that they were taking no medications that would affect gastric secretion, and, while all gastric bypass patients were receiving monthly intramuscular injections of vitamin B_{12}, none had received vitamin B_{12} supplementation within 2 weeks of the study.

Operation Technique

Using a standard midline approach to the upper abdomen and stomach, the gastric cardia was stapled across completely in a vertical direction using a double staple line (TA90B Stapler, Autosuture, US Surgical Corp.,

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Norwalk, CT) from the angle of His along the greater curvature to approximately 1 to 2 cm distal to the gastroesophageal junction along the lesser curvature (Fig. 1). The volume of the proximal gastric pouch so formed was approximately 10 mL. An 11-mm anastomosis to a Roux-en-Y limb was performed with a #21 end-to-end stapler (Autosuture, US Surgical Corp.).

Experiments

All studies were performed on an outpatient basis in our Gastroenterology Research Unit. After an overnight fast, subjects swallowed an 18-French modified orogastric sump tube with multiple side holes at the tip for aspiration and an infusion port located 5 cm proximally. With fluoroscopy, the tip of this tube was positioned within the gastric pouch (Fig. 2). The contents of the gastric pouch were aspirated, measured, and discarded. With the head of the bed elevated 15 degrees, 150 mM of NaCl containing 5 g/L of the nonabsorbable marker polyethylene glycol (PEG) was infused through the proximal infusion port at 2 mL/min; this infusion served to wash out the pouch and promote complete recovery of gastric secretion. Samples were collected continuously over the ensuing hour through the distal aspiration ports in four consecutive 15-minute intervals. Thereafter, pentagastrin (6 μg/kg) was given as a subcutaneous injection, and gastric samples were collected continuously in 15-minute intervals for 90 minutes. The orogastric tube was then removed.

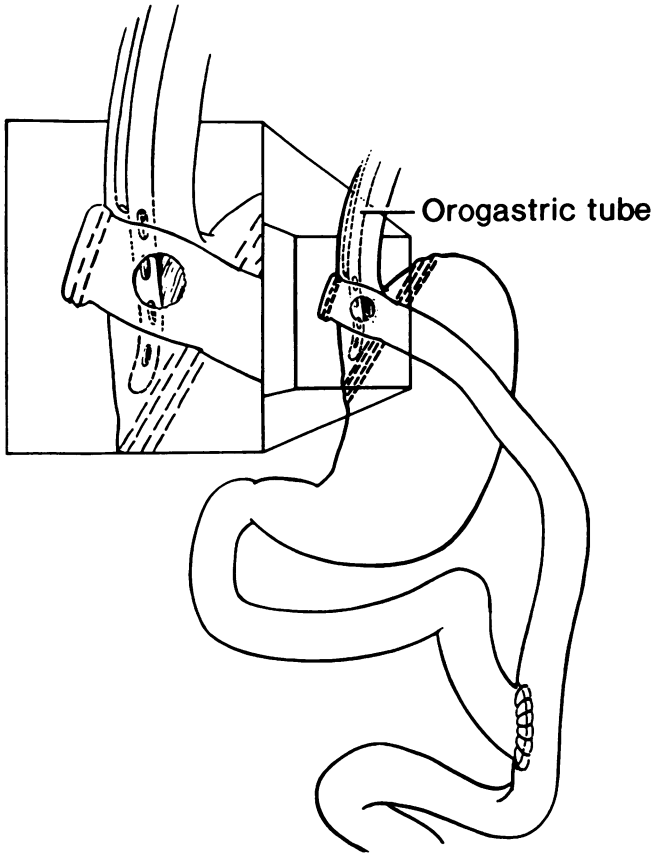

Figure 2. Orogastric tube assembly for measuring acid secretion after gastric bypass. The tip of the tube is positioned fluoroscopically in the stomach. The proximal port allows perfusion of a solution containing a nonabsorbable marker to allow quantification of the gastric aspiration from the distal ports. (Published with permission from the Mayo Foundation.)

After giving a baseline urine sample, each subject ingested in random order either 1 μg of crystalline (free) ^{57}Co-labeled cyanocobalamin (Mallinckrodt, St. Louis, MO) in 20 mL water or a food-bound ^{57}Co-labeled cyanocobalamin preparation incorporated into scrambled egg as described previously.[10] One milligram of nonradioactive vitamin B_{12} (Warner-Chillcott, Morris Plains, NJ) was then given by intramuscular injection as a "flushing" dose. Subjects collected the ensuing 24 hours of urine. Two days later, subjects ingested the other ^{57}Co-labeled cyanocobalamin preparation then received an intramuscular injection of nonradioactive cyanocobalamin and collected their urine for 24 hours.

Sample Analysis

The volume of each 15-minute gastric collection (basal and stimulated) was measured, and the concentration of PEG in each sample was determined using a turbidimetric method[11] on a spectrophotometer (Model 34, Beckman, Arlington Heights, IL). Per cent recovery of PEG was used to calculate the "corrected volume" of each gastric collection. An aliquot of each sample was titrated with 0.1 N NaOH to a pH of 7.0 to determine the acid (mEq) in the sample. Output of HCl (mEq/15 minutes) was calculated using the concentration of HCl in the aspirate multiplied by the corrected volume.

The volume of the 24-hour urine collection was measured, an aliquot was counted using a Picker well-type scintillation counter, and the per cent urinary excretion of ingested isotope was calculated.

Statistical Analysis of Data

The acid outputs of the four 15-minute basal collections were summed, and the basal acid output (mEq/hr) was calculated. The acid output for each of the six 15-minute pentagastrin-stimulated collections was analyzed, and the two consecutive poststimulation periods with the greatest acid outputs were added giving the peak acid output (mEq/30 minutes). Basal output, integrated output for the 90 minutes after pentagastrin, and peak-stimulated output were compared to those for 15 hospital age-/sex-matched control subjects without gastric dis-

ease using a two-sided Student's t test for unpaired data. The absorption (percentage of urinary excretion) of free and food-bound ^{57}Co-vitamin B_{12} in gastric bypass subjects was compared to that of 15 normal control subjects using the unpaired Student's t test. In addition, the correlation between acid secretion and vitamin B_{12} absorption in gastric bypass patients was assessed. Differences were considered to be significant if the p value was less than 0.05. Summary values in the text are represented as the mean ± SEM.

RESULTS

Acid Secretion

Acid output from the proximal gastric pouch in patients after gastric bypass was markedly less than acid output from the total stomach of age-/sex-matched hospitalized control subjects. Basal acid output in patients (0.01 ± 0.01 mEq/hr) was less than that in control subjects (5.0 ± 0.7 mEq/hr; $p < 0.001$), as was pentagastrin-stimulated peak output in patients (0.08 ± 0.04 mEq/30 min) *versus* control subjects (12.1 ± 1.3 mEq/30 min; $p < 0.001$) (Fig. 3A). Integrated acid output after pentagastrin was also less in patients (0.1 ± 0.04 mEq/90 min) than in control subjects (20.2 ± 2.3 mEq/90 min; $p < 0.001$) (Fig. 3B).

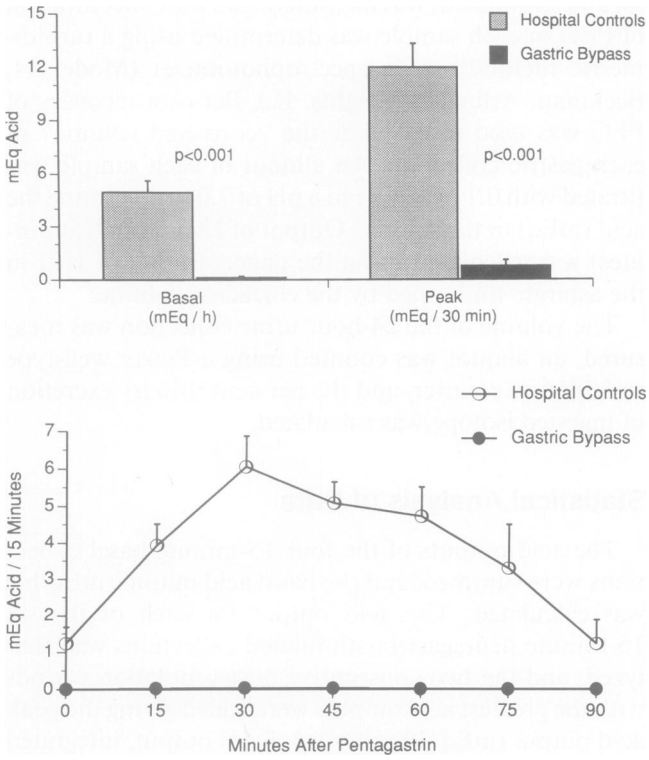

Figure 3. For gastric bypass patients and hospital control subjects, (A) basal and pentagastrin-stimulated acid output and (B) changes in acid output after pentagastrin stimulation (6 μg/kg subcutaneously).

Vitamin B_{12} Absorption

Although absorption of free vitamin B_{12} in subjects after gastric bypass was normal, absorption of food-bound vitamin B_{12} was abnormal (Fig. 4). Absorption (percentage of 24-hour urinary excretion) of free ^{57}Co-vitamin B_{12} was not different from that of healthy volunteers (11 ± 2% *vs.* 15 ± 2%, respectively; $p > 0.05$). In contrast, absorption of food-bound ^{57}Co-vitamin B_{12} was markedly lower in patients than in control subjects (0.8 ± 0.2% *vs.* 3.7 ± 0.5%; $p < 0.01$).

Correlation Between Acid Secretion and Vitamin B_{12} Absorption

Absorption of food-bound vitamin B_{12} was best correlated with basal acid output from the pouch (correlation coefficient $r = 0.752$), but not with pentagastrin-stimulated peak or integrated acid output ($r = 0.064$ and 0.355, respectively). Absorption of free vitamin B_{12} was not correlated with basal or pentagastrin-stimulated peak or integrated acid output from the pouch ($r = 0.373$, 0.361, and 0.523, respectively).

DISCUSSION

Although gastric bypass can be performed with low operative morbidity and mortality,[5] concerns remain about the long-term physiologic and nutritional consequences of this anatomic alteration. In the early experience with gastric bypass, the stomal ulceration rate varied from 3% to 8%.[12] Many of these ulcers developed in patients who had large proximal gastric pouches (> 50 mL). Subsequent investigators believed that by reducing the pouch size and thereby decreasing the acid secretion from this pouch, the ulcer rate would decrease. With the current techniques of minimizing the size of the proximal pouch to 50 mL or less, the rate of stomal ulcers reported in recent series still remains about 2%.[7,13] In a recent report, Jordan et al.[14] identified stomal ulcers in 34 of 412 (8.2%) patients after gastric bypass, two thirds of whom had staple line disruptions; this suggested that stomal ulceration occurred on an acid-mediated basis secondary to reflux of acid from the distal "bypassed" stomach into the proximal pouch and thus affected the acid-sensitive jejunal mucosa of the Roux limb. In contrast, 12 patients (3% overall) with stomal ulceration had intact staple lines, suggesting that the source of the acid was the proximal pouch itself. After our technique of vertical Roux-en-Y gastric bypass, we have shown clearly that with a very small proximal pouch con-

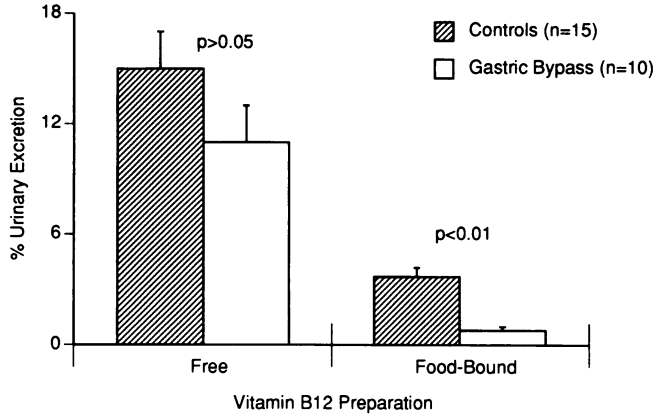

Figure 4. The percentage of ingested vitamin B_{12} (^{57}Co-cyanocobalamin) excreted in the urine over 24 hours after gastric bypass and in healthy control subjects.

structed from gastric cardia, acid secretion into the pouch is virtually absent. While this study has not addressed the incidence of stomal ulceration, these data suggest that with such limited acid secretion, acid-mediated complications such as stomal ulcers should be minimized, provided the staple line partitioning the stomach remains intact.

Altered acid secretion secondary to the gastric bypass anatomy may lead to vitamin B_{12} deficiency. Late after gastric bypass, 20% to 70% of patients have decreased serum vitamin B_{12} concentrations.[5,6,15–18] Clinically, long-standing vitamin B_{12} deficiency may result in devastating neurologic complications. The pathophysiology of this B_{12} deficiency is not known. Native vitamin B_{12}, as found in animal products, is bound tightly to proteins. Acid/peptic digestion is required for the intragastric release of vitamin B_{12} which only then can combine with the R-protein to form a complex. This vitamin B_{12}–R-protein complex is broken down in the duodenum, and the vitamin B_{12} release complexes with intrinsic factor (IF). The vitamin B_{12}–IF complex is then absorbed in the distal ileum through complex-specific receptors.[19,20]

Several explanations have been offered for vitamin B_{12} deficiency after gastric bypass for weight reduction:[15,21–23] (1) maldigestion of foods containing vitamin B_{12} (inadequate release of protein-bound vitamin B_{12} secondary to decreased acid/pepsin production from the proximal pouch); (2) decreased availability of IF caused by either degradation of unprotected free IF secreted into the bypassed distal stomach by luminal acid (IF–vitamin B_{12} complex is acid/pepsin stable), or poor mixing of IF from the distal stomach with the orally ingested vitamin B_{12}; (3) inadequate mixing of vitamin B_{12} with R-protein or the incomplete release of vitamin B_{12} from the vitamin B_{12}-R-protein complex; and (4) decreased formation of an IF–vitamin B_{12} complex owing to decreased or absent IF secreted into the proximal gastric pouch. Marcuard et al.[23] have presented evidence to support the latter hypothesis.

No studies have directly addressed the concept of maldigestion of food-bound vitamin B_{12} in patients after gastric bypass for weight reduction. Doscherholmen et al.[10,24,25] and others[26–28] have studied vitamin B_{12} absorption in patients with primary acid hyposecretion (pernicious anemia or simple gastric hypochlorhydria) or pharmacologically/surgically induced hypoacidity (antacid administration, H_2-receptor antagonists, partial gastrectomy, or vagotomy). These studies demonstrated abnormal absorption of protein-bound vitamin B_{12} when compared to crystalline (free) vitamin B_{12}, supporting the importance of acid/peptic-mediated liberation of dietary vitamin B_{12} to allow its subsequent absorption. Our study shows that normal amounts of the free, crystalline form of vitamin B_{12} are absorbed after gastric bypass. Therefore, the mechanism for absorption of free vitamin B_{12} must be adequate after Roux-en-Y gastric bypass (*i.e.*, there is adequate IF available and free vitamin B_{12} complexes with IF appropriately to be absorbed in the distal ileum). In contrast, there is a significant decrease in absorption of the naturally occurring food-bound vitamin B_{12}. Our observations implicate an inadequate release (maldigestion) of dietary vitamin B_{12} as the cause for the malabsorption in these patients, confirming the requirement for acid/peptic-mediated liberation of dietary vitamin B_{12} for subsequent absorption.

Our study, in conjunction with the studies of Doscherholmen et al.,[10,24,25] may have important physiologic implications in understanding the vitamin B_{12} malabsorption that accompanies certain disease states, such as pernicious anemia, or the postoperative states after partial gastrectomy. In the past, the presumed etiology of vitamin B_{12} malabsorption in these conditions was believed to be secondary to an inadequate secretion of intrinsic factor and thus the inability to absorb vitamin B_{12} in the ileum. Some individuals with documented vitamin B_{12} deficiencies, however, were observed to have normal findings of a Schilling test (*i.e.*, normal absorption of orally administered crystalline [free] vitamin B_{12}). This seeming paradox went largely unexplained. Our study supports the primary importance of acid/peptic-mediated liberation of vitamin B_{12} from its protein-bound state in food, as proposed by Doscherholmen et al.[25] In the absence of adequate acid secretion, the naturally occurring vitamin B_{12} as ingested in food remains protein-bound and thus unavailable for eventual complexing with the adequate amounts of IF secreted. This hypothesis would explain the normal findings of a Schilling test using orally administered, crystalline (free) vitamin B_{12} in the patient with clinical vitamin B_{12} deficiency.

The diagnosis of vitamin B_{12} deficiency after gastric bypass may be elusive because hepatic stores of vitamin B_{12} may prevent the development of a clinically significant serum deficiency for several years.[15,17,22] Some surgeons recommend prophylactic supplementation of parenteral vitamin B_{12} monthly in patients after gastric bypass. The data presented here suggest that orally administered, free vitamin B_{12} (crystalline vitamin B_{12} preparation) should result in absorption of normal amounts of vitamin B_{12} and may be used as supplementation for individuals after gastric bypass.

After vertical Roux-en-Y gastric bypass for morbid obesity, acid secretion into the gastric pouch is virtually absent. This technique should minimize the incidence of stomal ulcer. As a consequence of this operation, however, food-bound vitamin B_{12} is maldigested and subsequently not well-absorbed, while normal amounts of free vitamin B_{12} are absorbed. The results of this study suggest that postoperative vitamin B_{12} supplementation in patients after gastric bypass should be performed and possibly with orally administered crystalline vitamin B_{12}.

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