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Pancreatic and Intestinal Function Post Roux-en-Y Gastric Bypass Surgery for Obesity

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OBJECTIVES: Despite the fact that the most effective treatment for morbid obesity today is gastric bypass surgery, some patients develop life-threatening nutritional complications associated with their weight loss.

METHODS: Here we examine the influence of the altered anatomy and digestive physiology on pancreatic secretion and fat absorption. Thirteen post Roux-en-Y gastric bypass (RYGB) patients who had lost >100 lbs in the first year following surgery and who gave variable histories of gastrointestinal (GI) dysfunction, were selected for study. Food-stimulated pancreatic enzyme secretion and GI hormone responses were measured during 2 h perfusions of the Roux limb with a standard polymeric liquid formula diet and polyethylene glycol marker, with collections of secretions from the common channel distal to the anastomosis and blood testing. Fat absorption was then measured during a 72 h balance study when a normal diet was given containing ~100 g fat/d.

RESULTS: Result showed that all patients had some fat malabsorption, but eight had coefficients of fat absorption <80%, indicative of steatorrhea. This was associated with significantly lower feed-stimulated secretion rates of trypsin, amylase, and lipase, and higher plasma peptide-YY concentrations compared with healthy controls. Five steatorrhea patients were subsequently treated with low quantities of pancreatic enzyme supplements for 3 months, and then retested. The supplements were well tolerated, and fat absorption improved in four of five patients accompanied by an increase in lipase secretion, but body weight increased in only three. Postprandial breath hydrogen concentrations were elevated with some improvement following enzyme supplementation suggesting persistent bacterial overgrowth and decreased colonic fermentation.

CONCLUSIONS: Our investigations revealed a wide spectrum of gastrointestinal abnormalities, including fat malabsorption, impaired food stimulated pancreatic secretion, ileal brake stimulation, and bacterial overgrowth, in patients following RYGB which could be attributed to the breakdown of the normally highly orchestrated digestive anatomy and physiology.

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INTRODUCTION

The prevalence of class III obesity (BMI >40 kg/m^2, or morbid obesity) has increased nearly 10-fold since the late 1960s and doubled since the early 1990s,[1] now affecting ~35% of the male and female population.[2] As of 2002, an estimated 22% of US adults had the metabolic syndrome.[3] As of 2012, an estimated 33% of US adults had the metabolic syndrome.[4] Between 1996 and 2002, population adjusted rates of weight loss surgery increased >7-fold,[5] with an estimated 220,000 Americans undergoing weight loss procedures in 2008 (American Society for Metabolic and Bariatric Surgery. Fact sheet: http://www.asbs.org). The most popular technique today is the Roux-en-Y gastric bypass procedure (RYGB), which results in an average weight loss of ~95 lbs per year or a two out of three loss of the excess weight in 2 years.[6] Weight loss occurs for two major reasons: first, the volume of the stomach is reduced, and second, the duodenum and first part of the jejunum are bypassed resulting in malabsorption. However, alteration in GI anatomy results in a wide spectrum of changes in digestive and metabolic physiology, many of which can contribute to weight loss as recently reviewed by Madsbad *et al.*[7]

Although most patients tolerate the RYGB procedure remarkably well, with a leveling off of weight loss close to the ideal, about 10% over-swing and continue to lose weight or develop gastrointestinal or metabolic complications. The most serious GI complications are anastomotic ulceration and stenosis, intestinal obstruction, internal herniation and volvulus. In the extreme situation this can lead to loss of intestine, intestinal failure, and the need for home parenteral feeding and small bowel transplantation—a sadly ironic situation considering the original problem was a super-efficient digestive system. Metabolic complications such as acidosis, hepatic steatosis and liver failure possibly related to disturbance of the

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gut microbiome, can also be life threatening, but are less common today with the more conservative Roux lengths of 80–100 cm. Finally, it has recently become appreciated that a wide spectrum of micronutrient deficiencies, including low blood levels of iron, copper, zinc, selenium, thiamine, folate, and vitamins B12 and D, which are not usually monitored, are common and may contribute to impaired quality of life.[8]

Knowing that the physiology of digestion and absorption is highly integrated and orchestrated by neurohormonal mechanisms, we are concerned that the alteration of the normal anatomy could have profound effects on the normally highly integrated process of food-induced pancreatic stimulation and secretion.[9] The bypass removes the chief "intestinal phase" of pancreatic secretion mediated by food entering the duodenum and instead produces a state of permanent ileal brake stimulation as larger quantities of undigested food particles now enter the ileum. This results in the secretion of a number of peptides such as glucagon-like peptides 1 and 2, and peptide YY, which suppress pancreatic secretion,[10,11] thereby potentially exacerbating maldigestion and absorption.

The aim of the present study was to measure the pancreatic secretory response to feeding, in concert with food absorption in a select group of post-bypass patients referred to the University of Pittsburgh Medical Center (UPMC) Gastroenterology (GI) Division or the hospital Nutritional Support Service (NSS) for gastrointestinal or nutritional problems of variable severity. Second, we investigated whether patients who were shown to have high rates of fat malabsorption, i.e., $>20\%$, would benefit a 3-month course of pancreatic enzyme supplements.

METHODS

Patients. To date no studies have attempted to measure the effects of Roux-en-Y gastric bypass surgery (RYGB) on pancreatic secretion and fat absorption simultaneously. We therefore purposely selected a spectrum of patients, ranging from those who had successfully lost weight, had no major gastrointestinal symptoms, and did not exhibit micronutrient deficiencies, to those who had lost excessive weight and suffered from intermittent episodes of severe micronutrient deficiencies. Patients were selected from those with bypass referred to the GI or NSS hospital services. All had to satisfy the following *Inclusion criteria*: Adult patients with a history of RYGB, who gave a history of significant weight loss, intermittent micronutrient deficiencies, or diarrhea, were eligible if they had a history of morbid obesity, BMI >40 kg/m^2 before surgery, experienced weight loss of $>30\%$, or 100 lbs in 1st year following bypass surgery, and were able to consume normal requirement levels of food. *Exclusion criteria* included (1) any cause of chronic pancreatic dysfunction, such as chronic pancreatitis as evidenced by history, pancreatic imaging (CT or MRP scanning or ERCP), alcohol abuse (>3 units of alcohol/day), (2) intestinal resection other than RYGB, (3) impaired mucosa function due to the presence of chronic inflammatory bowel or chronic small intestinal mucosal disease confirmed by radiology and biopsy, and (4) unstable fluid and electrolyte balance and/or cardio-respiratory status (BP diastolic >100 mm Hg, systolic >200 or <80 mm Hg, ambient $pO_2<90\%$). Recruitment was continued until five patients with coefficients of fat absorption $<80\%$, the commonly used cut-off level for the definition of steatorrhea, had completed the 3-month pancreatic enzyme supplementation study. Results were evaluated by comparison to our previously published results from seven normal healthy volunteers given the same form of enteral feeding under similar conditions.[12] Informed signed consent was obtained from all participants, after the final protocol had been reviewed and approved by the University of Pittsburgh Institutional Review Board.

Study design. The study was divided into two phases. All patients satisfying the above criteria entered Phase 1, which consisted of the measurement of food-stimulated pancreatic secretion and 72 h fat absorption. Those found to have a coefficient of fat absorption $<80\%$, were invited to join Phase 2, where they were given pancreatic enzyme supplementation for 3 months and then restudied in the same way to assess whether pancreatic enzyme supplementation can improve digestive function, control gastrointestinal symptoms, and maintain nutritional status.

Phase I: measurement of the pancreatic secretory response to feeding. All subjects were admitted following an overnight fast to the University of Pittsburgh Clinical and Translational Research Center (CTRC) for the measurement of pancreatic enzyme secretion, followed by a 72-h fat absorption study while on a standard 100 g fat diet. The pancreatic secretory response to enteral feeding was measured as previously described in normal healthy controls following the placement of a double-lumen feeding tube system by transnasal endoscopy and fluoroscopic imaging with subsequent marker perfusion of the proximal duodenum followed by aspiration of duodenal contents 20 cm downstream.[13] In gastric bypass patients, this method had to be modified because of their altered gastrointestinal anatomy (Figure 1). In order to ensure full examination of the upper GI tract and Roux limb, an enteroscope was passed down to enter the "common limb" just distal to the Roux anastomosis.

First, the distance from the incisors to the gastroenterostomy was measured (x). Then the enteroscope was passed down to the Roux anastomosis and the distance again recorded (y). The length of the Roux limb was then calculated from $y–x$. The endoscope tip was then advanced distally down the common channel as far as possible and then a flexible ERCP-type guide wire (e.g., JAG-wire, Wilson-Cook, NC, USA) was passed through the endoscope and advanced under fluoroscopy to at least 30 cm past the Roux anastomosis. The enteroscope was carefully withdrawn, feeding the guide wire through at the same time to maintain distal position. A double lumen feeding tube system ("Kangaroo- Dobbhoff" system, Covidien-Kendall-Tyco Products, MA, USA), which has a 97 cm outer 16 French tube ("G-tube", used usually for gastroduodenal decompression) and an inner, adjustable, 170 cm 9 French jejunal tube (J-tube) was then passed over the per-oral guide wire with the J-tube in the withdrawn position. Under fluoroscopy, the G-tube was passed as far past the gastroenterostomy as possible, i.e., $\sim$95 cm (easy because the remaining stomach is minimal). The J-tube was then fed all the way down the Roux limb over the guide wire to $\sim$20 cm past the Roux anastomosis in the common channel.

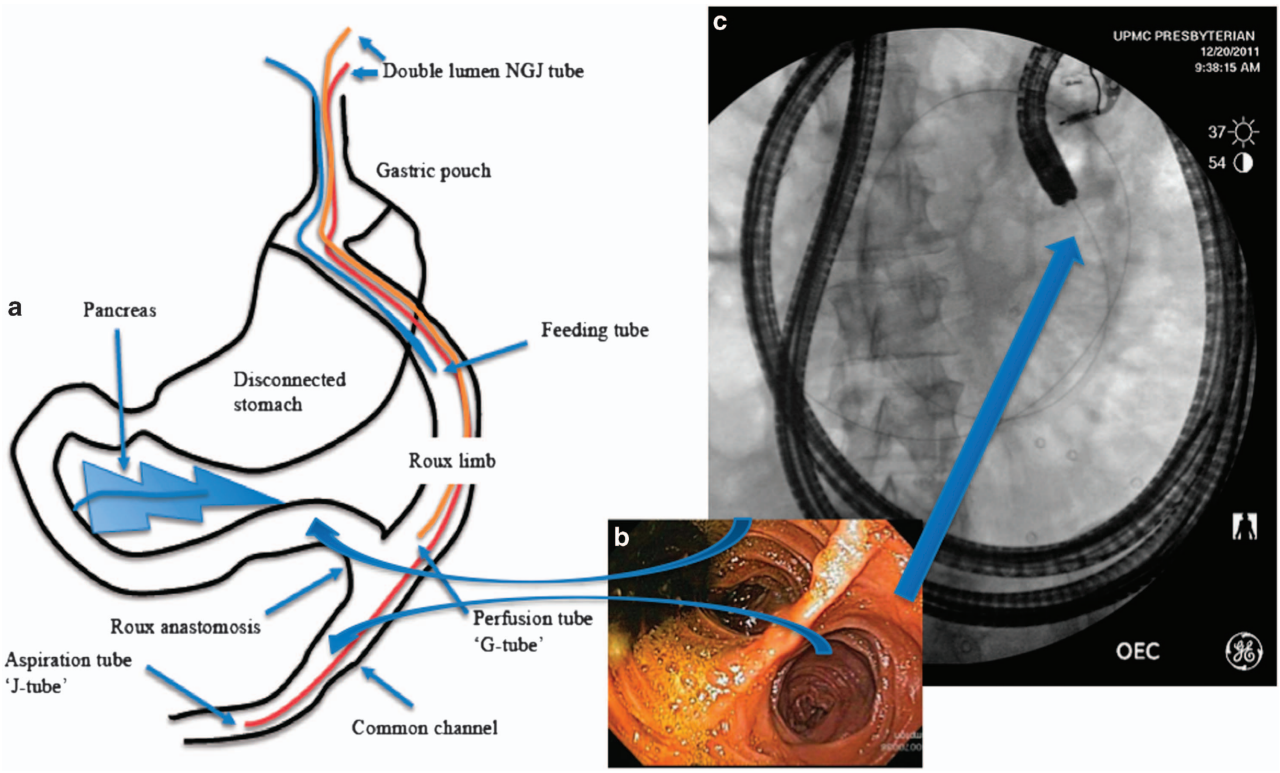

Figure 1 Positioning of the perfusion-aspiration tubes, and feeding tube for the measurement of pancreatic exocrine secretion (**a**) left panel. This was achieved by enteroscopy (**b**) middle photograph showing the Roux anastomosis, and fluoroscopy (**c**) radiograph upper right image and guide wire deployment. Blue arrows connect shared features of the three images.

Finally, a 10 French "duotube" (CORPAK MedSystems, Inc., Buffalo Grove, IL, USA) was fed transnasally into a position below the gastroenterostomy. The patient was then transferred back to the CTRC for the 2-h pancreatic secretion test. To do this, feeding with a balanced polymeric formula diet ("Ensure", Ross-Abbott Labs, Chicago, IL, USA) was commenced through the duotube at a constant rate for 2 h to provide normal nutritional requirements, i.e., 1.5 g protein and 40 kcal energy/kg ideal body weight/day. At the same time perfusion of the segment containing the Roux anastomosis was commenced through the G-tube with normal saline containing polyethylene glycol (PEG 3350 Da; 5 g/l) molecular weight marker at 300 ml/h, and the common post-Roux anastomosis channel tube was placed on low-intermittent suction. Aspirates were separated 15-min collections throughout the 2 h and divided into 5 ml aliquots. One sample was used to measure trypsin immediately in the lab, and the other treated with aprotinin protease inhibitor before being stored frozen at – 80 °C for the later measurement of amylase, lipase and PEG concentrations, as previously described.[13] While the anatomical position was different between patients and healthy controls, we are investigating digestion and absorption at the place where food and enzymes meet in both healthy volunteers and patients.

Calculations: secretion rates were calculated from the equation:

$$\textit{Pancreatic enzyme secretion}\ (U/h) = [\text{activ}(u/\text{ml}) \times \text{PEG}_{\text{in}}(g/l) \times \text{IR}(\text{ml}/h)] \div \text{PEG}_{\text{out}}(g/l)$$

where activ is the enzyme activity in the aspirate, PEG_{in} is the concentration of PEG in the perfusate, PEG_{out} is the PEG concentration in the intestinal aspirate and IR is the intestinal perfusion rate.[13]

Investigation of the ileal brake responses to feeding. During the feeding-stimulated pancreatic secretion study, venous blood samples were taken at 0, 60, and 120 min for measurement of plasma gastrin, cholecystokinin (CCK), peptide YY (PYY), and glucagon like peptide (GLP)-)-1 responses to feeding, as before.[12]

Measurement of 72 h Fat Absorption. Following completion of the secretion study, subjects remained in the CTRC and were given *ad lib* meals until midnight, then fasted until 0800 h, when they were asked to empty their bladders and bowels so that 72 h collections of urines and stools could be commenced. Over this period, they were given their usual diet, prepared individually by the CTRC dietitian, adjusted if necessary to contain ~100 g fat. Actual consumption rates were calculated by subsequent analysis of the types and quantities of foods consumed using a conventional computer software package. The urine and fecal collections were divided into three consecutive 24 h periods ending at 0800 h, when, again, patients were asked to force themselves to empty their bowels and bladders, but this time the outputs were included with the collections, as previously.[14,15] Total 72 h stool collections were weighed and then compounded into a single collection and sent to the hospital lab for routine

analysis of total fat content. To assess the effect of supplements on carbohydrate malabsorption and subsequent salvage by the colonic microbiota, we also measured breath hydrogen responses to the main midday meal at half-hourly intervals for 6 h during the 72 h fat absorption studies.[16]

Calculations

Coefficient of fat absorption (CFA)

$$= \frac{(\text{Fat}_{\text{diet}} - \text{Fat}_{\text{stool}}) \times 100\%}{\text{Fat}_{\text{diet}}}$$

Definition of clinically significant fat malabsorption. An abnormal CFA is $<95\%$.[17] However, for the purposes of this study, only patients with a CFA of $<80\%$, which is consistent with clinically significant fat malabsorption and steatorrhea, were eligible for Phase 2 three month pancreatic enzyme supplementation study.

Phase II: three month pancreatic enzyme supplementation study. On discharge from the CTRC, patients returned home to await the results of the fat absorption study. Patients shown to have a coefficient of fat absorption $<80\%$ were entered into the pancreatic enzyme supplementation study and given one month supplies with instructions to take 4 capsules of supplements with each meal (10,000 USP units of lipase per capsule), and 2 with snacks, to a maximum of 16 capsules per day, for 3 months to assess tolerance, clinical signs and weight change. This was the manufacturer's recommended starting dose for patients with pancreatic insufficiency. It provides, however, a lower quantity of lipase than that estimated to be secreted by the normal pancreas following a normal meal of 1,680,000 USP units, and is also lower than the lowest "normal" lipase output (2 SD below the mean) of 900,000 USP units per meal.[18] As Di Magno's classical studies suggested that only 10% of "normal" secretion was needed to prevent steatorrhea,[19] the absolute minimum dose to prevent fat malasorption due to pancreatic insufficiency would have been 90,000 USP units per meal, which is higher than the 40,000 units per meal we gave during the 3 month intervention. This conservative level of dosing was selected as the pathophysiology of gastric bypass malabsorption is quite different from that of chronic pancreatic insufficiency—on which the above requirement estimates were made—and we preferred to err on the low side for reasons of safety. The pancreatic enzyme supplement consisted of the currently commercially marketed product "Creon" (AbbVie, North Chicago, IL) which is an extract from porcine pancreas glands containing amylolytic, lipolytic and proteolytic activity, formulated as enteric-coated minimicrospheres. Each capsule delivers 10,000 USP units of lipase. The drug was manufactured by SPL Ltd, and supplied by Solvay under product investigational new drug (IND) 47546. As the use of supplements for gastric bypass patients was not one of the indications, we obtained our own IND for the study (76586). It should be noted that the currently available capsule that contains 12,000 USP units is considered equivalent, because of the practice of "overfilling" used with the older product. Chronic medications remained the same before and after supplementation. Finally, at the end of the 3 months, the pancreatic secretion and fat absorption investigations were repeated whilst receiving enzyme supplementation.

Progress was followed weekly by telephone, and by monthly visits to the Digestive Disease Clinic. At the end of this period, they were readmitted to the CTRC for repeat testing (i.e., as for Phase I) as above, but this time they were given enzyme supplementation 3 h before the pancreatic secretion study (4 capsules). During the 72 h fat absorption study, meals and snacks were supplemented with pancreatic enzymes as described above. Finally, breath hydrogen responses to the midday meal were again followed for 6 h.

Sample analysis

Pancreatic enzymes. Duodenal juice samples were prepared as previously for trypsin, amylase, and lipase activity measurement.[12] Trypsin was measured immediately in fresh samples, while amylase and lipase were measured in frozen samples preserved with trypsin inhibitor, aprotonin. The principle of the trypsin assay is based on the hydrolysis of N-benzoyl-L-arginine ethyl ester (BAEE) to N-benzoyl-L arginine (BA) and ethanol by trypsin in fresh intestinal secretions. Lipase and amylase were measured by simultaneous microplate technique in the UPMC Pathology laboratory using a Bio-Tek SynergyHT multi-detection microplate reader. The principle of the quantitation is the same, based on the ability of pancreatic enzymes within the juice samples to digest starch and triglyceride to produce colorimetric changes in metabolite complexes.

Gut peptides. Analysis was performed as we have described in healthy volunteers,[12] principally by radioimmunoassay in frozen plasma samples. Gastrin, CCK, GLP-1, and PYY were measured in Dr Holst's and Dr Rehlfeld's lab in Copenhagen, Denmark.

Statistical analysis. Results are presented as medians (range) for descriptive demographics and by group means (s.e.m.). Results in patients were evaluated by comparison to healthy volunteers, termed "controls" using StatView software to investigate our specific aims and explore our hypothesis that surgical modification of the GI tract could lead to maldigestion and malabsorption that may be reversed by pancreatic enzyme supplementation. The significance of the observed differences in group mean values was determined by Student's *t*-testing for unpaired data (e.g., patients vs. controls) if the data were normally distributed, or by Mann–Whitney rank sum test if not. Probabilities of <0.05 were accepted as significant.

RESULTS

Baseline demographic characteristics. Fifteen subjects were enrolled, but only 13 met criteria for study and were included in this analysis. Pre-bypass BMIs (body mass index) varied from 43 to 67 Kg/m^2 (Table 1). Time since bypass surgery ranged between 3 and 11 years. Eight had had cholecystectomies before bypass, and four hysterectomies.

Table 1 Demographic details of the post RYGB patients included in the study

Variable: median (range)	Study population ($n = 13$)	Healthy volunteers ($n = 7$)
Age: years	49 (22–58)	26 (22–45)
Sex, *n*		
Female	12	4
Male	1	3
Time since surgery, years	6.5 (3–10.75)	
Pre-op weight, Kg	131.1 (111.1–190.5)	
Pre-op BMI, Kg/m^2	48.8 (43.4–67.2)	
Weight loss in first year, Kg	52.3 (45.5–138.6)	
Weight on enrollment, Kg	68 (49–114)	80 (53–103)
BMI on enrollment, Kg/m^2	25.5 (16.9–42.5)	24.4 (18.6–32.0)

Numeric results given as group median and range in brackets
.

Table 2 Reported medical problems in the RYGB study cohort

	PRE-BYPASS	POST-BYPASS
Gastroesophageal Reflux	7	3
Asthma	3	4
Obstructive Sleep Dyspnoea	6	1
Anxiety Depression	4	7
Osteoarthritis	5	5
Metabolic Syndrome	5	2
Chronic Abdominal Pain	0	5
Diarrhea	0	6

Five were smokers, four had given up. Their initial weight loss varied from 45 to 138 kg in the first year. Five had been treated for anastomotic ulcers and three for internal hernias with the release of adhesions, without intestinal resection. After the first year, three regained and four continued to lose weight, such that at the time of enrollment in the study, one was underweight (BMI 16.4 Kg/m^2) and one remained obese (BMI >30).

Most patients expressed complex disease, with multiple complaints as summarized in Table 2, many of which pre-existed prior to bypass surgery. All gave a history of having intermittent bowel dysfunction for which they had sought help from gastroenterologists, six with chronic diarrhea. This was mild in four, but severe in two (#11 and #14). Patient #11 was noteworthy in that his stools were watery and contained undigested material and free oil (for detailed history and outcome, see below). Two had constipation associated with chronic abdominal pain, attributed to previous surgery, and narcotic use. Five suffered from chronic abdominal pain needing intermittent narcotics and six had chronic depression and/or anxiety.

Although all patients were shown to have elevated stool fats (i.e., >5 g/d), we had to enroll 13 patients before we could complete five subjects with CFA $<80\%$ through phase 2. It should be noted that 8 of the 13 were shown to have CFAs $<80\%$, but three either declined further study or dropped out of the Phase 2 enzyme supplementation study. One (#14), a 36-year-old woman with a past history of liver failure attributed to non-alcoholic steatohepatis with multiple micronutrient deficiencies had fat absorption $<50\%$. She was possibly the most chronically disabled of the patients studied, having recently been readmitted to the ICU with weight loss, mental status changes (sleepiness, confusion) associated with a desquamative dermatitis principally affecting the limbs and corners of the mouth. Blood tests revealed a wide range of vitamin and mineral deficiencies, including potassium, magnesium, zinc, iron, thiamine, nicotinamide, ascorbic acid, folate, B12, and vitamin D. A diagnosis of acrodermatitis enteropathica had been supported by skin biopsy (Figure 2).

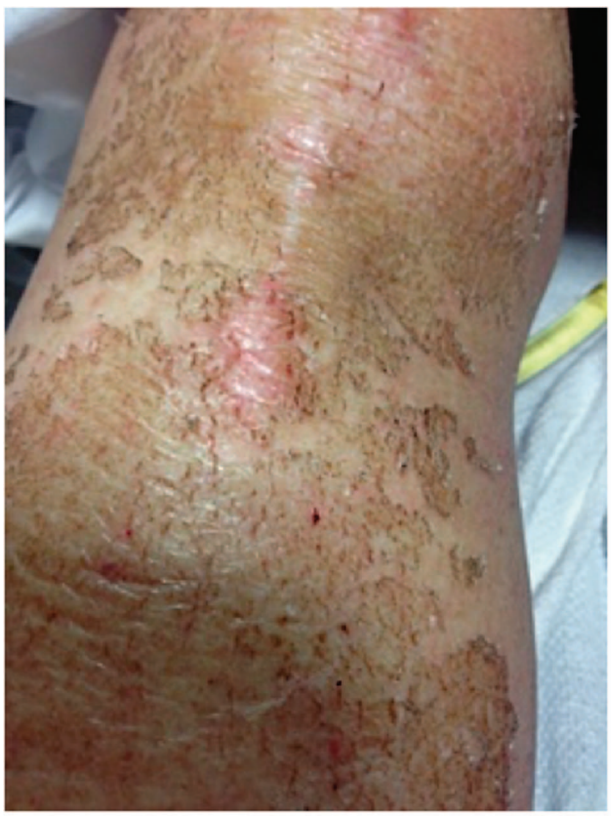

Figure 2 Desqamative skin lesions in patient #14. Biopsy confirmed a diagnosis of acrodermatitis enteropathica, associated with a wide range of vitamin and mineral deficiencies, including low plasma potassium, magnesium, zinc, iron, thiamine, nicotinamide, ascorbic acid, folate, B12, and vitamin D.

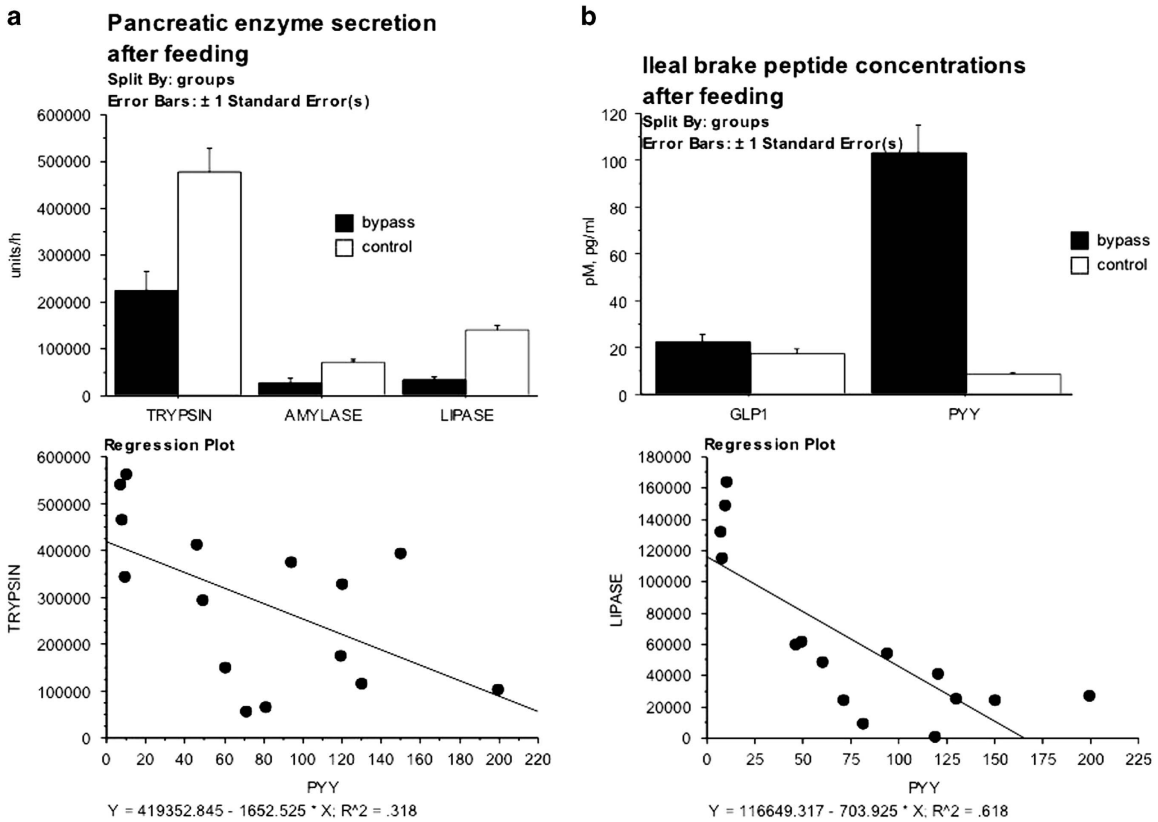

Figure 3 Illustration (group mean (s.e.m.)) of (**a**) the significantly lower enteral feed stimulated secretion rates of pancreatic trypsin ($P = 0.005$), amylase ($P = 0.008$), and lipase ($P < 0.0001$, upper panel left) and (**b**) higher plasma peptide-YY (PYY) levels ($P < 0.01$, left), but not CCK or GLP-1 levels, at each time point in RYGB patients compared to healthy controls. The lower left panel illustrates the significant negative correlation between trypsin secretion and plasma PYY responses measured at at 120 min into the infusion (r^2 0.618, $P = 0.0002$,). Lipase units Ku/h, PYY pg/ml.

She recovered quickly with a short course of parenteral nutrition, and was weaned successfully back on to a normal balanced diet supplemented with the micronutrients she had been deficient in, and discharged home. As she now satisfied the inclusion criteria, she was entered into Phase 1 of the study. Significant fat malabsorption was confirmed (stool fat 40 g/d), and she was commenced on pancreatic enzyme supplementation. Unfortunately, she was non-compliant and was unable to tolerate the supplements during her recurrent attacks of abdominal pain and chose not to return after 3 months for repeat testing. A further patient, #1, with a history of intermittent diarrhea, was mistakenly given 173 g fat per day during the baseline study, making it difficult to compare her responses to the other supplemented patients. The third patient, #4, declined continuation in the study for personal reasons.

Food-stimulated pancreatic secretion and GI peptide responses. We were able to aspirate sufficient serial secretions from the common channel in all but two patients, namely # 5 and #15, to measure secretion rates. In #5 the tube was partially dislodged in transport back to the research center and couldn't be repositioned. In #15, good position was achieved for the aspiration tube despite the Roux limb being exceptionally long (~200 cm). However, on both before and after enzyme supplement testing, no juice could be aspirated. This could be interpreted as zero secretion, but it was likely technical, and so we excluded this patient from the analysis. In the remaining patients, trypsin ($P = 0.005$ unpaired t test), amylase ($P = 0.008$) and lipase ($P < 0.0001$) secretion rates were significantly lower in patients than controls (Figure 3a). On the other hand, measurements of peptide-YY concentrations were higher ($P = 0.007$), while plasma CCK and GLP-1 were not (Figure 3b). The magnitude of the decrease in lipase was greatest for unexplained reasons. There was a significant ($P < 0.0001$) negative correlation between lipase (r^2 0.618, $P = 0.0002$) and trypsin (r^2 0.318, $P = 0.02$) pancreatic secretory responses and the plasma peptide-YY responses to feeding at 120 min (Figure 3c). Fasting PYY plasma concentrations were also significantly higher in patients with and without pancreatic enzyme supplementation (Figure 4).

72 h balance studies. Although we tried to keep each individual's fat intake to 100 g/d, dietary analysis (Table 3) showed that actual intake ranged from 73 to 173 g/d, the median being 98 g/d. All patients had increased stool fat quantities, ranging from 11 to 100 g/d. One patient (#11), with a history of internal hernia, weight loss and diarrhea, was

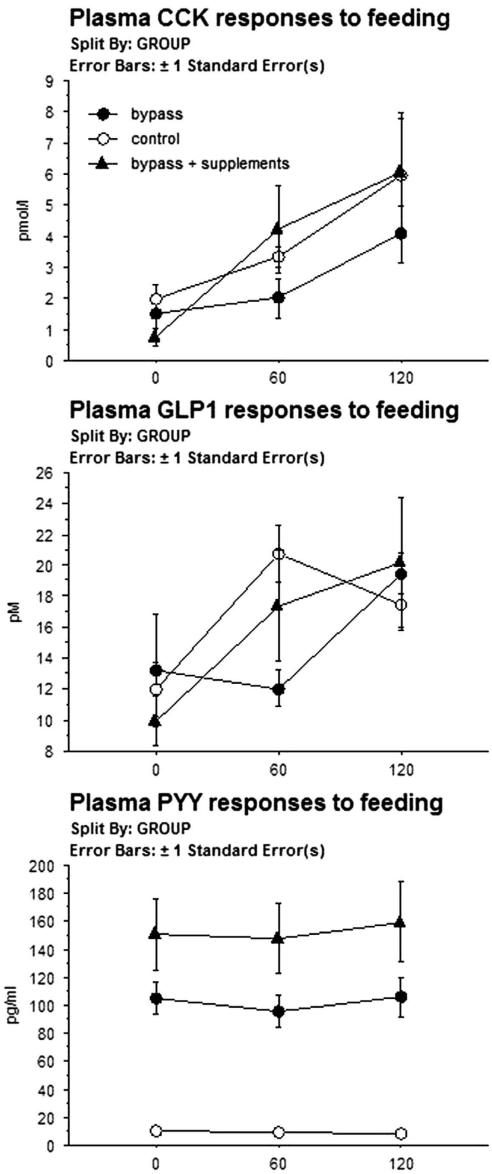

Figure 4 Changes in plasma gut peptide responses during the 2 h feed-stimulated pancreatic secretion study, illustrating the higher basal and food stimulated PYY concentrations in patients, which became even higher after pancreatic enzyme supplementation, with no significant change in CCK and GLP-1 levels.

remarkable in so far as he appeared to have no significant fat absorption (i.e., 6%, Table 3).

Sub-analysis of patients with coefficients of fat malabsorption <80%. Group mean stool fat quantities were 61 ± 13 g/d in those with CFA <80% and 23 ± 6 g/d in those with CFA >80%. No distinguishing factors were identified in the eight patients (Table 4) with coefficients of fat absorption less than 80%. For example, current body mass indices (28 ± 3 vs 26 ± 2 kg/m^2, respectively), length of the Roux limb measured at endoscopy (130 ± 20 vs. 137 ± 14 cm), time from surgery (64 ± 17 vs 81 ± 11 months), weight loss in the first year (119 ± 8 vs. 144 ± 24 lbs), GI symptoms, gut peptide and pancreatic enzyme responses to feeding, and urine

Table 3 Baseline (Phase 1) and post pancreatic enzyme supplementation (Phase 2) measurements of 72 h fat balance studies

Patient #	Phase	Stool weight g/24 h	Stool fat g/24 h	Diet fat g/24 h	Coefficient fat abs %
1	1	754	46	173	73[a]
2	1	1700	68	79	14[a]
2	2	820	33[b]	98	66
3	1	287	11	97	89
4	1	1354	47	73	36[a]
5	1	553	10	94	89
6	1	694	31	104	70[a]
6	2	699	26	100	74
7	1	300	11	100	89
8	1	2105	30	94	68[a]
8	2	1915	53	92	42
9	1	1384	11	100	89
11	1	7557	100	106	6[a]
11	2	5526	53	100	47
13	1	798	6	98	94
14	1	732	40	80	50[a]
15	1	1876	74	98	24[a]
15	2	464	17	100	83

Note 15 subjects were enrolled, and 13 met criteria for study and were included in this analysis.
[a]indicates those with coefficients of fat absorption <80% (steatorrhea).
[b]estimated from change in stool volume.

nitrogen losses (7.9 ± 2.8 vs. 9.1 ± 1.3 g/d) were all similar. Rates of amylase and lipase secretion were not significantly lower, and there was no significant correlation between lipase secretion and fecal fat excretion.

The effects of 3 months of pancreatic enzyme supplementation. The responses to pancreatic enzyme supplementation were variable. In general, the pancreatic enzyme supplements were well tolerated and stool fat excretion decreased in 4/5 (Table 3), and the group mean stool fat excretions decreased from 60.6 ± 13.4 to 36.6 ± 7.2 g/d, $P = 0.07$. Importantly, in the four who showed increases in fat absorption, the increases did not achieve the >80% cut off, indicating the malabsorption was not only caused by enzyme deficiency-maldigestion. Repeat pancreatic enzyme secretion testing after 3 months treatment showed a significant increase in lipase ($P = 0.027$) but not in trypsin and amylase secretion, and an increase in plasma PYY ($P = 0.0002$), but not in CCK, gastrin or GLP-1 responses (Table 4).

Body weight increased in three participants and decreased in two. One patient (#8, Table 4) complained that she experienced 'nausea when taking supplements with foods that did not contain fat', but body weight remained constant (1.1 kg loss after 3 months), and another (#2, Table 4) noted 'increased hunger and diarrhea' with the full dose, and so reduced the dosage to twice a day with meals with relief of these symptoms without weight loss (gained 1.5 kg). In three patients, stool frequency and consistency improved (#s 2, 8, 15), but in one (#11), frequent watery stools continued despite a reduction in stool fat from 100 to 53 g/d.

Breath hydrogen responses. Breath hydrogen responses were remarkably different compared with our previous

Table 4 Group mean (s.e.m.) changes in pancreatic enzyme secretion and plasma gut peptide responses to enteral feeding in five patients with coefficients of fat absorption <80 following pancreatic enzyme supplementation

	Gastric Bypass (GB)	GB plus supplements
Trypsin secretion Ku/h	241 (42)	279 (42)
Amylase secretion Ku/h	32 (8)	35 (7)
Lipase secretion Ku/h	35 (7)	191 (91)*
CCK pg/ml	2.2 (0.3)	3.6 (0.9)
Gastrin pg/ml	10.6 (1.7)	9.1 (1.6)
GLP-1 pM	15.1 (1.4)	15.9 (2.1)
PYY pg/ml	97.8 (6.3)	152.6 (14.2)*

*$p < 0.05$

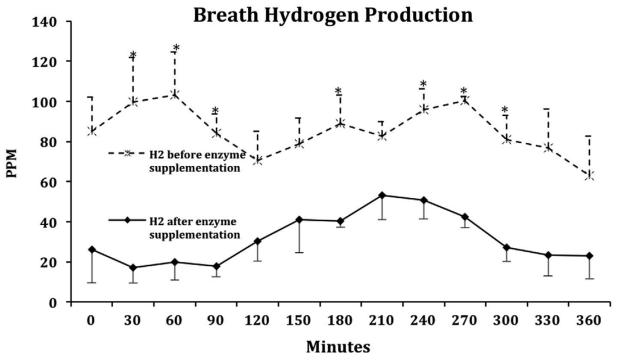

Figure 5 Changes in breath hydrogen responses to the midday meal following 3 months of pancreatic enzyme supplementation, showing significant suppression at multiple time points (*$P < 0.05$) and restoration of the normal biphasic pattern.

measurements in normal healthy subjects. In health, breath hydrogen concentrations are low after a meal and only begin to increase after 4–6 h, when carbohydrate residues (e.g., fiber) enter the colon and are fermented by the microbiota.[20,21] In sharp contrast, hydrogen concentrations were persistently high throughout the 6 h postprandial test indicating persistent activation of the microbiota (Figure 5). The early increase could be explained by bacterial overgrowth of the upper GI tract or rapid oro-colonic transit, and the late increase by carbohydrate malabsorption and increased colonic fermentation.[22]

Post study follow-up. The four patients (#s 2, 8, 11, 15) with coefficients of fat absorption <80% and who experienced reductions in diarrhea and/or improvements in fat absorption with enzyme supplements, were continued on the supplements off-study following completion of phase 2. All but one, patient #11, showed continued benefit. Patient 11 was remarkable as he continued to have severe diarrhea, with further weight loss and electrolyte deficiencies necessitating the intermittent use of parenteral nutrition at home. Colonoscopy appeared normal and so a capsule endoscopy was performed which suggested abnormal mucosa in the distal ileal common channel. A small bowel barium study supported the concern about ileal disease, showing a 20 cm stenotic segment. This patient gave a previous history of an internal small bowel hernia ("whole ileum and jejunum herniated through the retrojejunal space") 4 years following successful bypass and 2 years previously. Laparoscopy showed evidence of ischemia in the herniated bowel ("purple"), but decompression resulted in relief of ischemia ("pink") and his acute abdominal pain. Because of concern that the explanation for stenosis and continued diarrhea was chronic ischemia related to this problem, or other pathology of the ileum, our intestinal rehabilitation surgeons performed a laparotomy. Biopsy of the liver confirmed steatohepatis, but more relevantly they noted that "the terminal ileal loops were herniated into a huge mesenteric defect at the Roux anastomosis…", a finding they considered to unequivocally explain the patient's symptoms of intermittent obstruction, abdominal pain, and diarrhea. Indeed, these symptoms were relieved by repair of the hernia without the need for intestinal resection. Furthermore, he gained 10 kg, but 6 months later, he was admitted with acute pneumonia to the ICU and died expectantly of severe complicating adult respiratory distress syndrome.

DISCUSSION

Our study well illustrates the complex changes in digestive physiology and anatomy induced by Roux-en-Y gastric bypass surgery (RYGB) for obesity. Fat malabsorption of variable degrees was universal, confirming the view that weight loss can at least be partially explained by food malabsorption related to the shortened functional length of small intestine. Defining "clinically significant" fat malabsorption, or steatorrhea, as a coefficient of fat absorption <80%, 8 of the 13 fell into this category. Two of the thirteen gave a documented history of malabsorption measured by stool fat content, but in the remainder, it was asymptomatic and unrecognized. In the five patients in our study with steatorrhea who progressed to the three-month low dose pancreatic enzyme supplementation study, the effect was variable, with an increase in fat absorption in four, but an increase in body weight in only three. In the patient with the most severe fat malabsorption (#11), enzyme supplementation reduced stool fat losses 50%, but had little effect on the patient's chronic diarrhea and weight loss, which was later attributed to chronic intestinal ischemia in the common channel.

We are not aware of previous attempts to measure the pancreatic secretory responses to feeding in patients with RYGB. While this was technically challenging, we were able to recover sufficient post-Roux secretions and use standard marker correction techniques to assess overall secretory rates during the 2 h study in all but two patients. Calculated secretion rates of trypsin, lipase and amylase were well below those measured in healthy volunteers given the same form of feeding. It is possible that some of the difference could be due to technical differences related to the distortion and changed anatomy, but studies of ours have previously shown that the endoscopic aspiration of a single intestinal juice sample can provide information on the function of the pancreas.[23]

Our measurement of low feed-stimulated pancreatic enzyme secretion rates is novel and suggests a further mechanism, i.e., maldigestion, explaining fat malabsorption.

That this was not the primary cause of malabsorption was given by our observation that pancreatic enzyme supplements only increased fat absorption in four of the five treated patients, and even then did not normalize absorption. However, as discussed under Methods, the pancreatic enzyme supplements dose we used may well have been insufficient to reverse the maldigestion and malabsorption, particularly because all treated patients continued to have high stool fat excretions, despite the reductions. Further studies are warranted to determine whether higher dose supplementation, or a more dispersible non-enteric coated preparation combined with gastric acid suppression, could increase fat absorption further. Interestingly, lipase secretion in the five treated with pancreatic enzyme supplements increased significantly after the 3-month supplementation. The mechanism is unclear, but it could have been related to improved protein digestion and absorption resulting in improved pancreatic enzyme synthesis.[24]

The gastric bypass procedure has a major effect on the endocrine control of digestive physiology. Each segment of the intestine has a series of feedback loops that control the rate of secretion of digestive juice and migration of digesta through the absorptive areas. The passage of food into the upper GI tract stimulates pancreatic secretion to facilitate rapid digestion and absorption, whereas unabsorbed food entering the distal bowel inhibits secretion and motility to suppress fluid losses and prolong nutrient-mucosa contact time in order to maximize absorption. As shown on Figure 1, RYGB largely bypasses the gastric and intestinal phases of pancreatic stimulation and dumps undigested food into the ileum triggering the release of ileal brake peptides such as peptide-YY, GLP-I and GLP-2 from neuroendocrine L-cells in the distal bowel, which are responsible for the negative feedback, suppressing secretion and motility. The possibility that the low food-stimulated pancreatic enzyme secretion rates were related to "ileal brake" stimulation by malabsorbed nutrients was evidenced by the finding of significant elevations in peptide-YY (PYY) blood levels in the presence of normal cholecystokinin (CCK) responses, and the negative correlations between plasma PYY and pancreatic trypsin and lipase secretions at baseline. Human gut intubation studies have shown that the intraileal perfusion of lipids and amino acids inhibited pancreatic exocrine secretion,[10] and further studies have linked the suppression to the simultaneous release of PYY and glucagon like peptide 1 (GLP-1) from the entero-endocrine L-cells.[25] It is unclear why we failed to see an increase in GLP-1 in the current study, but the explanation might lie in the duration of study, as others have also noted increases in PYY but not GLP-1 in short term human ileal perfusion studies.[26] PYY has powerful antimotility effects on the proximal bowel,[11,25] which, together with GLP-1, may augment the role of the ileal brake in weight loss due to early satiety, adding a third explanation to the efficacy of RYGB in weight loss.[25,27,28,29] Others have demonstrated heightened PYY responses to feeding following RYGB. Chronaiou *et al* showed that PYY, and GLP-1 area under the curve responses to a mixed test meal remained higher at 3, 6, and 12 months in 12 post-RYGB patients compared with pre-surgery. Jacobson *et al* showed that the postprandial response to a mixed meal increased for C-peptide, GLP-1, GLP-2, PYY, CCK, and glucagon within 2 weeks of bypass surgery.[30,31] Finally, pancreatic polypeptide, another peptide linked to the ileal brake, provides an alternative mechanism through its ability to interfere with cholinergic transmission, which is the chief determinant of pancreatic stimulation and secretion,[32] supporting the conclusion that the ileal brake is a highly complex regulatory system affecting both upper GI motility and pancreatic secretion.

Another fascinating observation in our study was that PYY levels were already elevated before feeding in our study population. We have no explanation for this, as retained food was not found in the stomach during feeding tube placement under fasting conditions. Nor can we explain why levels increased further, at all time points, following three months of enzyme supplementation. If anything, improved digestion and absorption should reduce ileal brake stimulation. One point against the ileal brake theory was our finding of higher lipase secretion rates accompanied by higher plasma PYY responses following 3-months of pancreatic enzyme supplementation.

To the best of our knowledge, there are no publications of the effect of RYGB on microbial fermentation. Our measurements of increased fasting and fed breath hydrogen excretion rates suggested a general disturbance of gut function, possibly explained by small bowel bacterial overgrowth and increased colonic fermentation of malabsorbed carbohydrate and protein.[22] Dislocation of the digestive anatomy likely explains this through the lack of bacteriostatic gastric and biliary secretions in the upper small intestine and the increased flow of undigested carbohydrate into the colon. The suppression of breath hydrogen following oral pancreatic enzyme supplementation supports this suggestion. There is no easy way of treating small bowel bacterial overgrowth, as chronic antibiotic therapy has its own problems and can exacerbate diarrhea.[20]

The complexity of these changes, combined with the low "safe" dose of pancreatic enzyme supplements used, most likely explains our observations of a partial response to exogenous enzyme supplementation. The complexity might also explain why fat malabsorption was identified in all RYGB patients, even in those without symptoms. A further factor identified in one patient was the presence of distal intestinal dysfunction in the common "absorption" channel below the Roux anastomosis due to chronic ischemia due to chronic subacute volvulus associated with a large internal hernia. Our own unpublished experience is that this condition is not that uncommon after bypass surgery and often devastating, resulting in intestinal gangrene and subsequent intestinal failure due to short bowel, necessitating home parenteral nutrition. Some of these patients have deteriorated further with the development of liver failure, demanding a liver-small intestine transplant for survival.[33] In a recent review of the Pittsburgh and Cleveland Clinic experience, Abu-Elmagd *et al* described the outcomes of 142 post-bariatric surgery patients who developed intestinal failure. Twenty-three ended up needing visceral transplants. Nutritional autonomy was achieved by transplantation in 83%. Twenty-three percent went on to become obese again, well illustrating the point that the gut is not the culprit of the initial problem.

The most recent Cochran review of bariatric surgery identified 22 usable studies, which included 1,798 patients, followed up generally for only 1–3 years[34]—unlike our study population who were between 3 and 11 years post bypass surgery. While weight loss was well reported, and some studies measured glucose and lipid responses and quality of life, no comparative analyses of specific nutritional outcomes were evaluable. The reviewers concluded that "……while there was good evidence for sustained weight loss, adverse events were poorly reported and follow-up was generally far too short, i.e., 1 to 2 years, therefore the long term effects of surgery remain unclear".

A series of recent studies have highlighted the fact that while gastric bypass patients can appear to be doing well, multiple micronutrient abnormalities are often present, including deficiency of iron, copper, zinc, selenium, thiamine, folate, and vitamins B 12 and D.[8] Unfortunately, these parameters were not closely monitored in our patients, as the problem was not recognized at the time the study was designed. The amalgamation of these apparently "subclinical" deficiencies can be expected to compromise physical and mental well-being. This might account for the observation that while RGBY appears to improve quality of life during the first and second year following surgery—when the influence of weight loss is predominant—by 4 years, only general health and functional capacity parameters remained better.[34] The true depth of these micronutrient deficiencies is likely underestimated, as blood levels commonly do not reflect cellular deficiency and consequent organ functional impairment.

Our results add new information on the detrimental effects of RYGB on the normally highly orchestrated processes of digestion and absorption. For example, the digestive process is generally $>95\%$ efficient as the secretion of digestive enzymes by the pancreas occurs in three phases, the cephalic, the gastric, and the intestinal phases, to ensure orderly food breakdown, fluid and enzyme secretion, sterilization and finally thorough mixing of the digesta to maximize enzyme activity and food hydrolysis to release absorbable elemental nutrients.[35] Bypassing much of the upper GI tract results in loss of gastric and the intestinal phase of pancreatic secretion, and dislocation of the inflow of pancreobiliary secretions into the distal small intestine results in impairment of mixing of food and enzymes, disturbed neuroendocrine control, loss of the migrating motor complexes, stasis and small bowel bacterial overgrowth. Furthermore, the heightened flow of undigested food particles into the distal bowel produces chronic stimulation of the ileal brake, which exacerbates the impairment of gastric, pancreatic, and biliary secretions.

In conclusion, our study highlights the fact that while RYGB is remarkably successful in achieving sustained weight loss and the removal of the metabolic complications associated with morbid obesity, it unties the functional anatomy of the human gut and digestive physiology that has taken millions of years of evolution to achieve. If these alterations are compounded by additional medical or surgical complications, a state of intestinal failure can result, culminating in the loss of essential nutrients and life-threatening complications. For these reasons, alteration of the digestive system to control obesity cannot be considered the long-term solution as there is nothing wrong with the gut in the first place: in fact it could be argued that obesity is a consequence of a super-efficient digestive system. The problem is in central command: irrespective of whether the obesity is a consequence of over-eating or low metabolic expenditure rates, the condition can be cured by reduced eating, and negative energy balance. Consequently, the optimal treatment and prevention of obesity will have to be the development of new more potent methods of suppressing appetite and controlling food intake so that digestive physiology can be preserved to prevent potentially serious nutritional-metabolic and surgical complications. Until such time as this goal is achieved, bariatric surgery will, however, remain the most effective way of reducing the morbidity associated with extreme, class III obesity. However, our results indicate the need for a vigilant nutritional and metabolic follow up, even in patients who have few symptoms to report. In those with intermittent diarrhea, continued weight loss, or micronutrient deficiencies, a therapeutic trial of pancreatic enzyme supplements could be justified to counterbalance possible ileal brake driven maldigestion.

CONFLICT OF INTEREST

Guarantor of the article: Dr O'Keefe accepts full responsibility for the conduct of the study. He has access to the data and control of the decision to publish.

Specific author contributions: Stephen J D O'Keefe was involved in planning and conducting the study, collecting and interpreting data, and drafting the manuscript. He approved the final draft submitted. Tina Rakitt helped with conducting the study, collecting and interpreting data, and drafting the manuscript. She approved the final draft submitted. Junhai Ou was involved with conducting the study, collecting and interpreting data, and drafting the manuscript. He approved the final draft submitted. Ihab El Hajj, Elizabeth Blaney, and Kishore Vipperla all helped with the conduct of the study, the collection of samples, interpretation of the data, and drafting of the manuscript. Ihab El Hajj, Elizabeth Blaney, and Kishore Vipperla approved the final draft submitted. Jens-Jules Holst and Jens Rehlfeld helped with the study design and analysis of gut peptide samples, and their interpretation. Jens-Jules Holst and Jens Rehlfeld approved the final draft submitted.

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Potential competing interests: None. No conflicts of interest were noted for any of the authors.

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MD, MPH, FACS, director of minimally invasive bariatric and general surgery at UPMC, with study design.

Study-Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Morbid obesity (BMI >40 kg/m^2) now affects approximately 35% of the USA population.
- ✓ The most effective current treatment is gastric bypass surgery.
- ✓ Roux-en-Y gastric bypass surgery is effective principally due to suppressed food consumption, but mild malabsorption may also occur.
- ✓ Malabsorption is due to the shortened length of the "common channel" of small intestine.

WHAT IS NEW HERE

- ✓ Some patients develop severe fat malabsorption, i.e., steatorrhea, following Roux-en-Y gastric bypass surgery for obesity.
- ✓ Fat malabsorption was associated with suppressed pancreatic enzyme secretory responses to feeding.
- ✓ The reduced pancreatic secretory responses to feeding were associated with increased ileal brake peptide (GLP-1, peptide-YY) responses.
- ✓ Pancreatic enzyme supplementation reduced steatorrhea in some patients.

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