Nephrolithiasis After Bariatric Surgery for Obesity

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Summary: Surgical intervention has become an accepted therapeutic alternative for the patient with medically complicated obesity. Multiple investigators have reported significant and sustained weight loss after bariatric surgery that is associated with improvement of many weight-related medical comorbidities, and statistically significant decreased overall mortality for surgically treated as compared with medically treated subjects. Although the Roux-en-Y gastric bypass (RYGB) is considered an acceptably safe treatment, an increasing number of patients are being recognized with nephrolithiasis after this, the most common bariatric surgery currently performed. The main risk factor appears to be hyperoxaluria, although low urine volume and citrate concentrations may contribute. The incidence of these urinary risk factors among the total post-RYGB population is unknown, but may be more than previously suspected based on small pilot studies. The etiology of the hyperoxaluria is unknown, but may be related to subtle and seemingly subclinical fat malabsorption. Clearly, further study is needed, especially to define better treatment options than the standard advice for a low-fat, low-oxalate diet, and use of calcium as an oxalate binder.

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As much as 20% of the US population currently is classified as obese (body mass index [BMI] $>$ 30 kg/m^2), including 11.5 million who are morbidly obese (BMI $>$ 40 kg/m^2).[1] Of these, up to 5 million Americans have what is deemed medically complicated obesity because they have weight-related comorbidities such as concurrent diabetes mellitus, hypertension, sleep apnea, or other severe weight-related conditions. Because diet and lifestyle interventions have been disappointing for durable weight loss, increasing numbers of patients choose surgical interventions to treat their illness.[2–7] Indeed, most currently performed bariatric procedures result in marked and sustained weight loss, associated with improvements in abnormal glucose homeostasis, insulin resistance, sleep apnea, hypertension, and cardiovascular risk factors.[8–13] Of these, Roux-en-Y Gastric bypass (RYGB) procedures are performed most commonly in the United States.[5] Two very recent studies confirm an overall benefit for weight loss and overall mortality among those who undergo bariatric surgery.[14,15] In 1991 a National Institutes of Health conference deemed a BMI greater than 40 kg/m^2 an indication for bariatric surgery. In addition, patients with a BMI greater than 35 kg/m^2 plus a weight-related medical condition such as diabetes were considered good candidates.[16] The recent trend has been to broaden these eligibility criteria even further to consider other less extreme comorbidities such as obstructive sleep apnea and severe lymph edema when contemplating a surgical treatment.[17]

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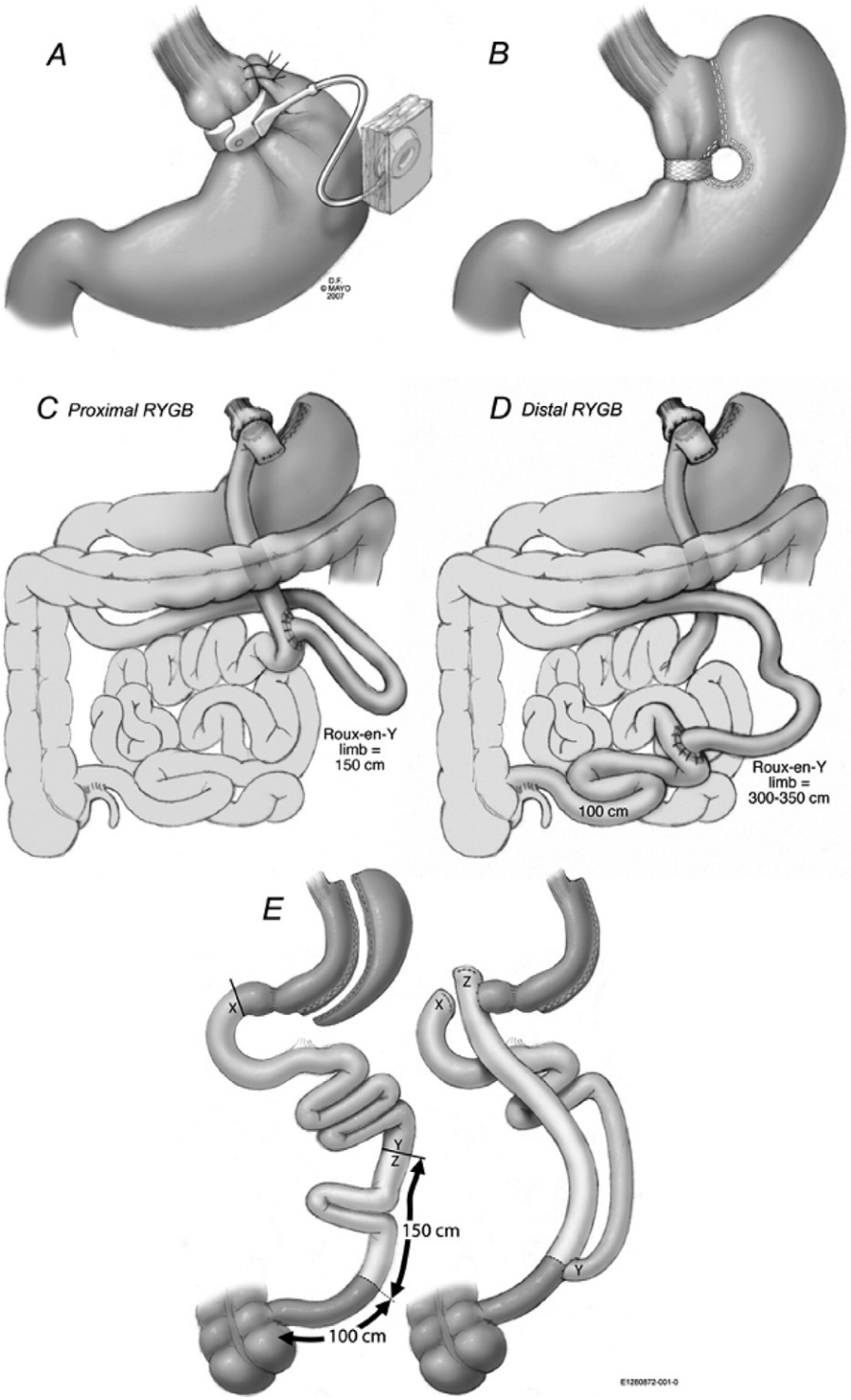

Figure 1. Commonly used weight loss procedures. (A) LAGB, (B) VBG, (C) proximal RYGB, (D) distal RYGB, and (E) BPD with the duodenal switch. See text for discussion of each procedure.

SURGICAL OPTIONS FOR OBESITY TREATMENT

The bariatric procedures currently used promote weight loss via varied mechanisms (Fig. 1). Restrictive procedures such as vertical banded gastroplasty (VBG) and laparoscopic adjustable gastric band (LAGB) each limit caloric intake by the physical restriction imposed by the band on

dietary intake. The VBG consists of a stapled proximal gastric pouch with a fixed and nonadjustable outlet created by a mesh band or Silastic (Dow Corning, Midland, MI) ring. Although still performed, poor long-term outcomes for weight loss and maintenance have led many bariatric surgeons to abandon this procedure.[7,18,19] LAGB consists of 2 components, a silicone gastric band with an inner inflatable cuff and a reservoir connected by tubing. The band is placed around the gastric cardia to create a 15-mL proximal gastric pouch with an adjustable restrictive outlet connected to the reservoir implanted in the subcutaneous tissue of the abdominal wall. Access to the reservoir with the ability to add or remove saline allows modification of the dietary restriction imposed[18,20] (Fig. 1). The biliopancreatic diversion (BPD) with the duodenal switch promotes weight loss by causing malabsorption of nutrients. The first portion of the duodenum is transected with resection of the greater curvature of the stomach, leaving a 100- to 150-mL lesser curvature–based gastric sleeve with an intact antrum and pylorus. The proximal ileum is divided 250 cm from the ileocecal junction, and the biliopancreatic limb is anastomosed to the distal ileum creating a short (100-cm) common channel. Then, duodenoileostomy anastomosis is made by bringing the Roux limb up to the gastric sleeve (Fig. 1).[18]

By far, the most common bariatric surgery offered is the RYGB, a procedure that promotes weight loss by both dietary restrictions that result from the formation of a small (10-30 mL) gastric pouch, and maldigestion of nutrients from formation of a gastrojejunal anastomosis with a Roux limb promoting a dumping physiology. The length of the Roux limb can vary from 75 (proximal RYGB) to longer than 200 cm (distal RYGB). The longer the Roux limb, the greater the role of malabsorption of nutrients as a mechanism for weight loss (Fig. 1).[18] Because studies suggest that RYGB results in greater and more sustained long-term weight loss with acceptable risks, it is currently the more widely performed procedure,[21] although preferences and frequencies of various procedures are very center-specific.

COMPLICATIONS OF OBESITY SURGERY

The current bariatric procedures have been deemed relatively safe and effective, even though both short-term and long-term complications have been recognized, including osteopenia, osteomalacia, and, more rarely, neurologic disorders.[22–28] Overall morbidity rates vary from 10% to 23% depending on the surgical procedure performed, although these have been declining as a result of increased attention being paid to potential metabolic consequences (eg, calcium and other micronutrient status).[8,29] However, until very recently an increased risk of nephrolithiasis was not considered a potential risk.[30] Mortality rates reported are less than 1% with the current procedures, although higher mortality rates have been reported among Medicare beneficiaries.[31] Importantly, 2 recent studies strongly suggested long-term mortality benefits for recipients of both restrictive and gastric bypass procedures, compared with unoperated, control obese subjects.[14,15]

HYPEROXALURIA AFTER JEJUNOILEAL BYPASS: LESSONS FROM THE PAST

Historically, nephrolithiasis was a well-recognized complication of bariatric surgery. In particular the development of calcium oxalate stones was a serious complication of jejunoileal (JI) bypass surgery performed in the 1970s for the management of obesity and hypercholesterolemia. This risk for nephrolithiasis, renal failure, and other life-threatening complications such as liver disease led to the abandonment of this surgery more than 20 years ago.[32]

The best evidence regarding the true risk of complications from this procedure comes from a single center report in the mid-1990s.[33] In this study, 453 patients were followed up long term after JI bypass. The risk of renal complications increased linearly over 15 years to ultimately reach an incidence of nephrolithiasis of 28.7% and of renal insufficiency of 9.0%. These alarming data suggest that the risk of complications from modern RYGB may be cumulative as well, especially as years at risk begin to accumulate among the large number of patients who recently have undergone this newer procedure. Even if the prevalence of hyperoxaluria, stones,

and renal damage is less than after JI bypass, the total number of cases could be substantial because only about 25,000 JI bypass procedures were completed in the United States before the procedure was discontinued in the early 1980s, whereas 103,000 RYGB surgeries were completed in the United States during 2003 alone.[34] A more recent study has confirmed that long-standing JI bypass patients have marked hyperoxaluria, relative hypercalciuria, low urinary citrate levels, and normal urine volumes.[35] The net effect is a marked increase in calcium oxalate supersaturation, and the patients produce almost entirely calcium oxalate stones, a few of which contain a small percentage of uric acid.[35]

The mechanisms of hyperoxaluria were relatively well described during the 1970s and 1980s among patients with intestinal diseases associated with fat malabsorption, including post-JI bypass. Early studies confirmed, as suspected, that the increased urinary oxalate came from dietary sources because it could be prevented via use of a strict, very low oxalate diet.[36] Among patients with ileal resection and fat malabsorption, the amount of urinary oxalate excretion correlated linearly with fecal fat content,[37] and in individual patients fecal fat excretion, gastrointestinal absorption of labeled oxalate, and urinary oxalate excretion all decreased when they were placed on a low-fat diet.[38] Therefore, abnormal delivery of fat to the colon appears to be a key feature of this disorder that has been termed *enteric hyperoxaluria*.

Intracolonic calcium concentrations also appear to be a key determinant of oxalate absorption in the colon. In a small but intriguing study, calcium was infused directly into the colon of 3 patients with surgical resections, fat malabsorption, and enteric hyperoxaluria.[37] Although the diets were not changed, and fecal fat remained constant, urinary oxalate levels decreased, and then promptly reverted to baseline when the calcium infusions were stopped. One cannot usually infuse calcium directly into the colon, but oral administration of calcium supplements will increase calcium delivery to the colon because only a fraction will be absorbed. When JI bypass patients were placed on a higher-calcium diet (3,000 vs 800 mg), gastrointestinal absorption of oxalate decreased and urinary oxalate levels similarly decreased.[39] Similar findings were documented on a 3,000-mg versus a 250-mg calcium diet.[40] In the latter study, even though urinary oxalate decreased, urinary calcium levels also increased on the higher-calcium diet. The net effect of these countervailing changes on urinary supersaturation for calcium oxalate was not assessed, and therefore increased urinary calcium excretion while on high doses of oral calcium used as an oxalate binder remains a potential concern, and potentially could neutralize any positive effect. In future studies, it will be important to carefully consider the net effect of oral calcium on urinary calcium oxalate supersaturation, in addition to urinary oxalate levels alone.

Based on these older published data the standard treatment of this patient group has been a low-fat, low-oxalate diet with the use of calcium supplements as an oxalate binder. If urinary citrate levels are reduced, the use of oral potassium citrate also makes sense. Fortunately, data suggest that reversal of the JI bypass, even many years out from the procedure, often can halt a decline in kidney function, and in many cases result in some modest longer-term improvement, as well as stop progression of the stone disease.[41] Therefore, it still is important to identify long-term JI bypass patients with this complication because treatment options exist.

RENAL STONES AFTER RYGB

Little is known about the impact of most currently offered bariatric surgeries on the risk for nephrolithiasis. Because obesity and insulin resistance have been implicated as risk factors for nephrolithiasis, especially uric acid stones, one might reasonably hypothesize that RYGB could ameliorate kidney stone risk.[8,29] Further, the RYGB surgery with a Roux limb less than 150 cm in length generally has been believed not to cause fat malabsorption, thought to be a critical factor in the development of enteric hyperoxaluria.

However, we recently noted a seemingly large number of patients with calcium oxalate stones and relatively marked hyperoxaluria after RYGB in our institution. Therefore, in 2005 we conducted a systematic review of all Mayo

Clinic patient records to identify potential cases of enteric hyperoxaluria in patients who had received RYGB between 1984 and 2005 (n = 1,436).[30] In addition, a survey was sent to the subgroup that had undergone the potentially more malabsorptive distal RYGB (Roux limb, ~300 cm; common channel length, ~125 cm; n = 258), because we hypothesized that those patients might be more susceptible to this complication. A total of 23 cases of enteric hyperoxaluria were identified by the initial record review, 14 after proximal RYGB and 9 after distal RYGB. Most concerning were 2 patients who presented with renal failure and biopsy-proven oxalate nephropathy. Neither had a prior history of renal disease or nephrolithiasis. Among the distal RYGB group, 188 of 258 patients returned the supplemental survey. Of these, 27 (16%) had experienced nephrolithiasis after the procedure; only 8 had a stone preoperatively. We cannot reliably estimate the prevalence of stones in the proximal RYGB because they were not surveyed, many of these patients do not receive regular medical care at Mayo, and renal stones are not always recorded in the medical record. However, this study did suggest that nephrolithiasis was common after RYGB, and perhaps more so in the distal RYGB group.

In early 2006, we updated the Mayo Clinic series to include an increasing number of patients referred to our stone clinic after RYGB, and for whom we had detailed metabolic data.[42] A total of 60 patients were identified, including 31 who had been seen in the Stone Clinic. A large percentage (55%; 17 of 31) had been seen for the first time in the stone clinic over the prior 2 years. The mean BMI of patients preoperatively was 57 kg/m^2, with a decrease of 20 kg/m^2 at the time of the first stone event, which averaged 2.9 years after RYGB. Although the distal RYGB accounts for only approximately 18% of the total RYGB procedures performed at Mayo, there were 36 distal RYGB and 24 proximal RYGB patients identified. Therefore, patients may be at greater risk for stones after the distal procedure. Among those analyzed, stones were 100% calcium oxalate in 19 patients, and mixed uric acid/calcium oxalate in 2 other instances.

Among the subset seen at the Mayo stone clinic, hyperoxaluria was observed commonly (present in 17 of 31), with a mean urine oxalate of 0.66 mmol/d (Table 1). Urinary citrate and calcium were reduced modestly, and overall urinary supersaturation for calcium oxalate was quite high. When divided into proximal and distal patients, there was no significant difference in urinary parameters (Table 1). However, there did seem to be differences in the urine composition, depending on the time of presentation after RYGB. Those who presented less than 6 months postoperatively rarely had increased urinary oxalate (mean, 0.44 mmol/d), whereas those who presented more than 6 months out often did (mean, 0.77 mmol/d; Fig. 2). Urinary supersaturation was equally high in both groups, however (Fig. 2), in large part owing to low urine volumes in the less than 6 months group. These differences may reflect changes in gastrointestinal function and diet that developed over the first year after the procedure.

HYPEROXALURIA AFTER RYGB

To get a better sense regarding how common hyperoxaluria might be in the total group of patients who undergo RYGB, we next completed a small pilot study of patients randomly selected before (n = 20), 6 months after (n = 8), and 12 months after (n = 13) proximal RYGB. At baseline hyperoxaluria was rare (mean oxalate, 0.35 mmol/d), and urinary calcium oxalate supersaturation was not increased above the reference mean (Fig. 3). Urinary composition was not changed significantly in the 6-month postoperative group, but by 12 months the mean urinary oxalate (0.74 mmol/d) and calcium oxalate supersaturation were both increased in this group of non–stone-forming patients. Other urinary changes included a modest decrease in urinary citrate and calcium (Table 1 and Fig. 3). These data suggest that many patients may have subclinical enteric hyperoxaluria and may be at risk for stones after standard RYGB because more than half (7 of 13) were hyperoxaluric and nearly all (12 of 13) had increased calcium oxalate supersaturation at the 12-month time point.

Other data are emerging that link RYGB to kidney stones. A very recent report listed urinary tract calculus as a common cause for emer-

Table 1. Urinary Chemistries in Patients With and Without Gastric Bypass Surgery

	Asplin and Coe[45]					
	Normal		Stone Formers		JI Bypass	
	Male (n = 96)	Female (n = 72)	Male (n = 1,330)	Female (n = 718)	Male (n = 17)	Female (n = 10)
Oxalate, mg/d	37	28	42	33	109	96
Calcium, mg/d	187	150	237	192	135	95
Citrate, mg/d	497	607	529	506	202	341
pH	6.06	6.03	5.99	6.05	5.63	5.54
Volume, L/d	1.52	1.41	1.74	1.50	1.97	1.73
SS CaOx	8.1	6.6	9.1	8.9	8.8	9.0

gency room visits (3.6%) and readmission to the hospital (3.0%) within the first 180 days after bariatric surgery.[43] The University of Pittsburgh also recently examined their longer-term experience with a specific focus on stone prevalence.[44] The medical records of a total of 972 persons who underwent RYGB between the years of 1997 and 2004 at their bariatric surgery center were examined for stone events, including a review of radiology reports. In their group, 85 patients (8.8%) had a preoperative stone history. Of these, 26 (31.4%) had recurrent stones postoperatively (mean time, 1.9 y), whereas an additional 31 developed stones de novo at a mean time of 2.8 years (3.5%). These data may underestimate the scope of the problem because stone history was obtained from record review alone and no information was provided regarding time or extent of follow-up evaluation in the cohort. Nevertheless, the data did suggest that stone prevalence was enriched by at least 70% in this population, compared with expected rates derived from Nutrition Examination Survey III data.[44]

Recently, a large referral laboratory reported urinary chemistry values for 132 patients who were identified as having undergone modern bariatric surgery for obesity.[45] Only an abbreviated patient history was available; for example, the subtype of surgery (eg, banding vs gastric bypass) was not known. Nevertheless, the urinary data are remarkably similar to those observed in our patient group at Mayo Clinic. The mean urine oxalate for men and women was

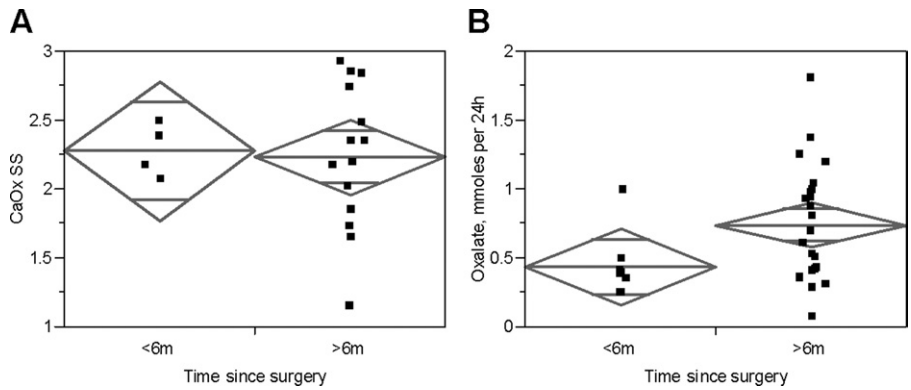

Figure 2. Urine oxalate excretion and calcium oxalate supersaturation among those stone formers who present early (<6 mo) or late (>6 mo) after RYGB. (A) Hyperoxaluria was more prominent among those who presented later, (B) although calcium oxalate supersaturation was equally high in the less than 6 month group, largely owing to lower urine volumes.

Table 1. Urinary Chemistries in Patients With and Without Gastric Bypass Surgery (Continued)

		Sinha et al[42]			
Modern Bariatric		RYGB With Stones	RYGB: Cross-Section		
Male (n = 28)	Female (n = 104)	(n = 31)	Preoperatively (n = 20)	6 mo (n = 8)	12 mo (n = 13)
92	73	65	34	31	73
140	143	132	206	111	112
524	396	394	660	563	444
5.71	5.75	5.6	5.95	5.81	5.76
1.75	1.52	1.61	1.93	1.41	1.63
10.6	13.6	8.2	4.0	4.3	6.9

increased (83 mg/d), with a corresponding increase in urinary calcium oxalate supersaturation (Table 1). Urine calcium excretion was reduced slightly, although citrate excretion and total volume both were fairly normal. Urine oxalate excretion was not as high as in an older group with JI bypass; nevertheless, the calcium oxalate supersaturation was actually marginally

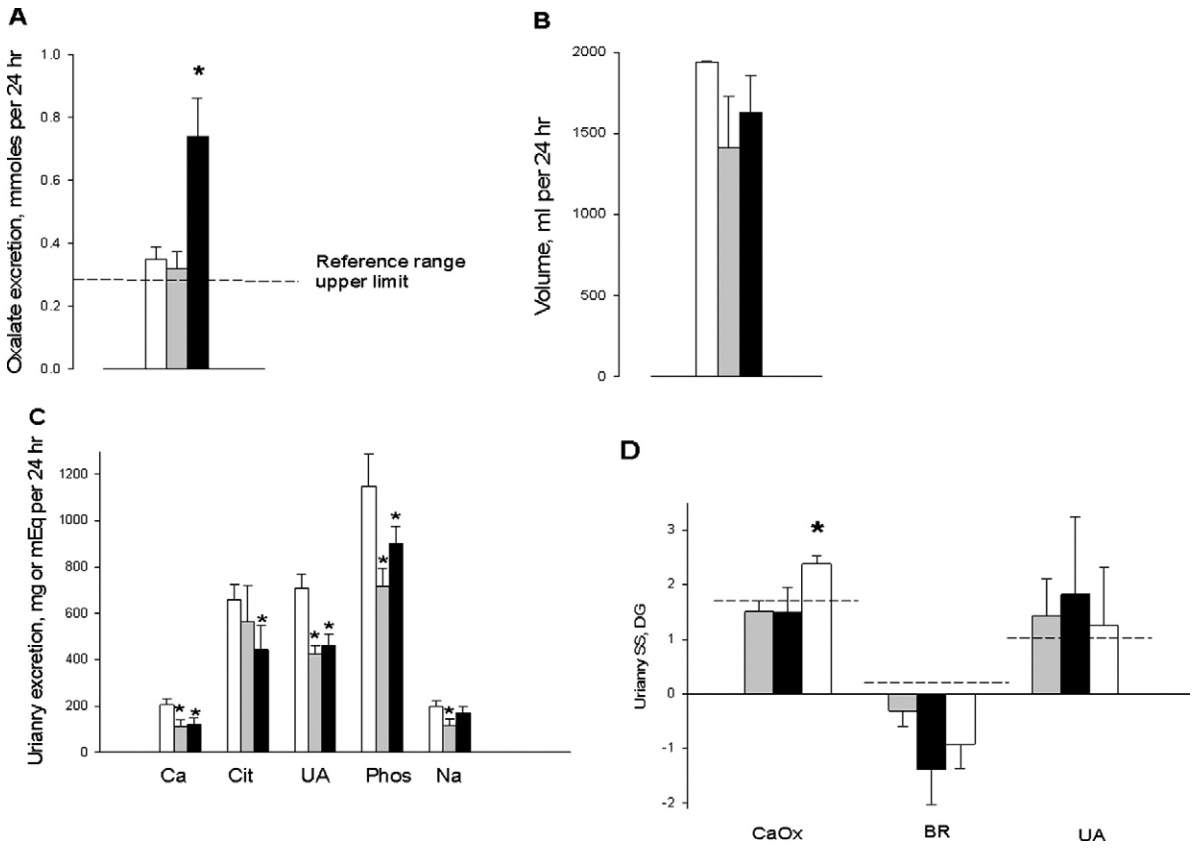

Figure 3. Urine chemistries among a random sampling of patients before (n = 20), 6 months after (n = 8), and 12 months after (n = 13) RYGB. (A) Hyperoxaluria was common at 12 but not at 6 months, (D) with a corresponding increase in urinary calcium oxalate supersaturation. (B) Urine volume, and (C) citrate and calcium excretions also decreased postoperatively. These data suggest that many patients may be at risk for calcium oxalate stones after this procedure. □, Baseline; ▨, 6 months; ■, 12 months. * $P < 0.05$ *v* baseline.

higher in the modern bariatric group. Importantly, 23% of this referral laboratory cohort had a daily urinary oxalate excretion of greater than 100 mg, a level at which renal damage has been well described. The time to first stone also was comparable with the Mayo cohort (3.6 vs 2.9 y), although relatively fewer had pre-existing stones (1 of 132 vs 11 of 31).

To our knowledge, no information currently is available to assess the relative potential risk for nephrolithiasis and/or hyperoxaluria after the various forms of bariatric surgery. However, very limited data are available regarding the degree of fat malabsorption in patients after selected procedures.[34] After JI bypass the overall fat absorption was reported to be only 15%, whereas it was 97% after VBG or LAGB. Fat absorption also was compromised severely after BPD, with or without duodenal switch (19%) and intermediate after RYGB (67%). Based on these data, one might hypothesize that the risk for enteric hyperoxaluria would be greatest after BPD, lowest for VBG or LAGB, and intermediate for RYGB. However, even these inferences are tentative because the fat absorption numbers were based on measurements in only 9 patients in the RYGB group. We do note, however, that even though patients in the RYGB group had an increased average of 44 grams of fecal fat (vs 139 g in the BPD groups) the patients did not report prominent symptoms of diarrhea (average, 1.5 bowel movements/d vs 3.6 in the BPD groups). This observation correlates with our personal clinical experience that the RYGB patients rarely report clinical diarrhea.

TREATMENT OF NEPHROLITHIASIS AFTER RYGB

Typical treatment strategies for enteric hyperoxaluria, as described earlier, are prescription of a low-fat, low-oxalate diet, generous fluid intake, use of oral oxalate binders such as calcium, and potassium citrate as a crystallization inhibitor. In practice, these dietary modifications may be quite difficult to implement. For example, many patients have learned to alter their eating patterns after RYGB and consume many small meals and/or snacks to avoid dumping symptoms. The use of oxalate binders can be quite difficult under these circumstances. Although in general oxalate is found in green leafy vegetables, chocolate, nuts, strawberries, and soy products,[46] accurate information regarding the oxalate content in particular foods is difficult to find because it is not measured routinely or listed on food labels. In addition, published values are general estimates because oxalate content can vary depending on conditions during growth or manufacturing. Therefore, avoiding high oxalate intake can require extensive education and patient motivation.

It is known that endogenous intestinal flora can metabolize oxalate.[47] For example, a subset of the population is colonized with *Oxalobacter formigenes*, an obligate anaerobe that uses oxalate as its sole energy source. Several studies have suggested that colonization with *O formigenes* is associated with lower urinary oxalate excretion, and that loss of colonization (eg, as a result of antibiotic use) can increase urinary oxalate levels.[48,49] Whether or not RYGB procures alter colonization with this organism is unknown, however, a single study showed decreased intestinal colonization with these oxalate-degrading bacteria in patients after JI bypass.[50] Other intestinal bacteria also could alter oxalate fluxes, either via degradation within the lumen or effects on mucosal permeability and/or active absorption. A recent study showed that oral administration of a mixed preparation of lactic acid bacteria with in vitro oxalate-degrading capacity reduced urinary oxalate excretion by a small but significant percentage in a group of patients with enteric hyperoxaluria.[51] Oral administration of *O formigenes* or its active oxalate-degrading enzymes represents another promising treatment strategy because rats colonized with *O formigenes* changed from net colonic absorbers of oxalate to net secretors.[52] A recent study supported the potential use of such a strategy.[53] In a small group of patients with primary hyperoxaluria, a genetic disorder characterized by hepatic overproduction of oxalate, somewhat surprisingly an oral preparation of *O formigenes* reduced both plasma oxalate concentrations and urinary oxalate excretions. Given the pathophysiology of the hyperoxaluria in these patients, one must speculate that increased colonic metabolism of

oxalate resulted in increased net secretion of oxalate into the gastrointestinal tract, and hence its elimination from the body. These exciting results will require confirmation in larger and more diverse patient populations, but nevertheless provide intriguing insights into a novel treatment strategy.

CONCLUSIONS AND FUTURE DIRECTIONS

As a first step, it will be vital to define the scope of the problem. How common is hyperoxaluria after RYGB or other forms of bariatric surgery? How many of these patients develop stones and/or renal damage? Based on the preliminary data described earlier, it seems likely that the prevalence of hyperoxaluria and nephrolithiasis will be significant. Therefore, studies that can identify improved strategies to decrease urinary oxalate levels among the ever-expanding pool of patients undergoing RYGB surgery clearly are needed. Initially, it will be important to precisely determine the mechanism of hyperoxaluria in these patients. Is it strictly related to fat malabsorption? Are other factors involved, for example, altered colonization with oxalate-degrading bacteria? Once these factors are identified, careful treatment trials with known or novel therapeutic agents are needed. Oral administration of oxalate-degrading bacteria, purified enzymes, or newly developed oxalate-binding resins all seem feasible. In addition, because recent evidence suggests the intestinal anionic transporter *SLC*26A6 is a key mediator of intestinal oxalate secretion,[54] this membrane protein has emerged as an intriguing target for the development of a drug that could enhance elimination of oxalate by the intestinal route.

If the incidence and severity of enteric hyperoxaluria described earlier is confirmed in prospective evaluations of larger numbers of post-RYGB patients, preventative treatment strategies may be necessary in all patients after the surgery. In the meantime, as a minimum, all patients who develop renal stones after RYGB should undergo prompt metabolic evaluation with initiation of appropriate treatments for stone prevention. Given the overall evidence that RYGB and other bariatric surgical procedures seem to benefit morbidly obese individuals,[14,15] we do not currently consider the risk for hyperoxaluria and nephrolithiasis to be a contraindication for these surgeries. Rather, physicians caring for these patients need to be aware of this potential complication, factor it in when weighing the pros and cons of a surgical intervention in an individual patient, and have a low threshold to screen for its development postoperatively.

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