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KIDNEY STONE INCIDENCE AND METABOLIC URINARY CHANGES AFTER MODERN BARIATRIC SURGERY: REVIEW OF CLINICAL STUDIES, EXPERIMENTAL MODELS, AND PREVENTION STRATEGIES

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Abstract

Bariatric surgery has been associated with increased metabolic kidney stone risk and post-operative stone formation. A MEDLINE search, performed for articles published between January 2005 and November 2013, identified 24 pertinent studies containing 683 bariatric patients with 24-hour urine profiles, 6,777 bariatric patients with kidney stone incidence, and 7,089 non-stone forming controls. Of all procedures reviewed, only Roux-en-Y gastric bypass (RYGB) was linked to post-operative kidney stone development, increasing stone incidence two-fold in non-stone formers (8.5%) and four-fold in patients with previous stone history (16.7%). High quality evidence from 7 studies (n=277 patients) before and after RYGB identified the following post-RYGB urinary lithogenic risk factors: 30% reduction in urine volume (the main driver of urinary crystal saturation), 40% reduction in urinary citrate (a potent stone inhibitor), and 50% increase in urinary oxalate (a stone promotor). Based on this, a summary of strategies to reduce calcium oxalate stone risk following RYGB is provided. Furthermore, recent experimental RYGB studies are assessed for insights into the pathophysiology of oxalate handling, and the literature in gut anion (oxalate) transport is reviewed. Finally, as a potential probiotic therapy for hyperoxaluria, primary data from our laboratory is presented, demonstrating a 70% reduction in urinary oxalate levels in four experimental RYGB animals after colonization with *Oxalobacter formigines*, a non-pathogenic gut commensal that uses oxalate as an energy source.

Overall, urine profiles and kidney stone risk following bariatric surgery appear modifiable by dietary adjustments, appropriate supplementation, and lifestyle changes. For hyperoxaluria resistant to dietary oxalate restriction and calcium binding, well-designed human investigations

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are needed to identify additional means of lowering urinary oxalate, such as *Oxalobacter* colonization or empiric pyridoxine therapy. Further investigations are also needed to determine tolerability and compliance of stone prevention strategies, such as citrate supplementation and hydration, in this population.

Keywords

morbid obesity; gastric bypass surgery; nephrolithiasis; kidney stone; calcium oxalate supersaturation; hyperoxaluria; hypocitraturia; metabolic acidosis

INTRODUCTION

Obesity in the US is an overwhelming clinical problem, with recent estimates suggesting over a third of American adults are obese (body mass index [BMI] >30 kg/m²), including more than 15 million who are considered morbidly obese (BMI >40 kg/m²)⁽¹⁻³⁾. For these patients, medical weight loss tends to be either temporary or completely ineffective. To date, bariatric surgery is the most effective means of long-term weight loss, curing obesity-related diabetes and hypertension as well as lowering cardiovascular and overall mortality risk in this population^(4, 5). These successes have led to a 6-fold increase in bariatric surgery in the United States over the last 10 years, from 36,700 procedures in year 2000 to 220,000 procedures in year 2009^(4, 6).

In 2005, Nelson *et al* first described the renal complications of hyperoxaluria, calcium oxalate stones, and oxalate nephropathy in a select group of 23 patients following Roux-en-Y gastric bypass (RYGB) surgery⁽⁷⁾. Since that report, more than 30 different publications have attempted to examine the potential metabolic derangements that raise kidney stone risk following bariatric surgery. In this review, published data detailing urinary chemistry profiles and kidney stone incidence following bariatric surgery are tabulated and summarized. Recent experimental data from human and animal studies that offer insight into the pathophysiology of stone risk will be critically examined, and a summary of recommendations that may reduce kidney stone risk in bariatric, stone-forming patients will be provided.

LITERATURE REVIEW METHODS

Published studies were searched from electronic databases including Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE, and EMBASE. Reference lists were also made from bariatric surgery and urology textbooks as well as review articles. The search terms included all forms and abbreviations of nephrolithiasis, kidney stone formation, calcium oxalate supersaturation, and hyperoxaluria in regard to restrictive bariatric procedures, laparoscopic adjustable gastric banding (LAGB) and sleeve gastrectomy (SG), and malabsorptive bariatric procedures, biliopancreatic diversion with duodenal switch (BPD) and Roux-en-Y gastric bypass (RYGB) surgery. With the assumption that the reader is familiar with the technical nuances of each of these procedures, detailed differences among them will not be included in this review. Of the 31 clinical articles identified, 8 were excluded due to being case reports or bariatric case series

containing less than 8 patients. The remaining studies containing pertinent clinical stone incidence and urine profiling (n=24) or basic science experimentation were reviewed and summarized either in tables or within text. Although no data exists in the bariatric surgery arena, a brief review of enteric oxalate transporters is included within the basic science section of the text.

URINARY CHEMISTRY PROFILES AFTER BARIATRIC SURGERY

Prospectively collected, 24-hour urine chemistry profiles from primarily non-stone formers before and after either RYGB or BPD procedure are summarized in Table 1 and detailed in supplemental Table S1. No studies with this stringent prospective design were identified in LAGB or SG patients. At a mean of 11 months post-RYGB, 277 patients were identified to have, on average, increased urinary oxalate levels from mean 28 mg/day to 44 mg/day on home diets (Table 1). Urine calcium oxalate supersaturation (CaOx SS), a calculated predictor of kidney stone risk that should be <2, increased from baseline of 1.5 to 2.3 post-operatively. In addition to increased urinary oxalate excretion and CaOx SS, Park *et al* (2009) also noted RYGB patients had decreased urinary citrate and total urine volume when compared to their pre-operative urine samples ⁽⁸⁾. Citrate, a potent endogenous inhibitor of calcium oxalate stone formation, can reduce CaOx SS by forming soluble complexes with calcium ⁽⁹⁾. Although there were no symptomatic stone events after a mean of 9.6 study months in these patients, the authors of this study suggest that chronic acidosis may have led to decreased urinary citrate, further increasing stone risk ⁽⁸⁾.

Similarly, Duffey *et al* (2010) described a doubling of urinary oxalate excretion and significant decreases in urinary citrate excretion in a two year, prospective study in RYGB non-stone forming patients ⁽¹⁰⁾. Furthermore, their study importantly showed that risk of post-operative hyperoxaluria appears to increase over time, not decrease or remain stable ⁽¹⁰⁾. To examine this hyperoxaluria phenomenon more closely, Kumar and colleagues ⁽¹¹⁾ tested plasma and urinary oxalate, fecal fat excretion, and response to oral oxalate load in 9 pre- and post-RYGB and 2 pre- and post-BPD morbidly-obese patients. At 12 months post-op, they found a 25% increase in urine oxalate, a 60% increase in plasma oxalate (p=0.016), a two-fold increase in calcium oxalate supersaturation (p=0.003) and fecal fat excretion (p=0.26), and a dramatic 50% increase in urine oxalate following oxalate load (p<0.02) ⁽¹¹⁾, suggesting that hyperabsorption of dietary oxalate from the GI tract may increase stone risk (see enteric hyperoxaluria in pathophysiology section).

Recently, three groups have described the temporal changes in CaOx SS in the early post-operative period after RYGB. Wu *et al* (2013) noted urinary changes 6 months after RYGB (n=38) compared to baseline, including significant increases in urinary oxalate excretion, calcium, and CaOx SS (using the “relative supersaturation scale” from 5–10) and decreases in total urine volume ⁽¹²⁾. The lack of hypocitraturia and presence of hypercalciuria in this cohort, compared to previous studies, was judged to be due to increased utilization of calcium citrate supplementation in their patients post-operatively ⁽¹²⁾. Agarwal *et al* (2013) evaluated 24 hour urines in 13 patients before and at time points 1, 2, 4, and 6 months after RYGB ⁽¹³⁾. Using a variety of standardized in-house assays and one private hospital-based laboratory, they noted a doubling of urinary oxalate starting at month 2 through month 6

($p=0.005$), a 40% reduction in urinary citrate at month 6 ($p=0.4$), and 30–60% reduction in urinary volume ($p<0.001$) that started in the immediate post-operative month ⁽¹³⁾. Lastly, Valezi *et al* (2013) studied the pre- to postoperative changes in urinary metabolites in 151 patients after RYGB, 16 of whom had previous stone disease ⁽¹⁴⁾. At one year, urinary oxalate levels increased 37% (mean 24 mg/day to 41 mg/day, $p<0.001$) while decreases in both urine citrate (36%; mean 268 mg/day to 170 mg/day, $p<0.001$) and urine volume (29%; 1.3 liters/day to 0.9 liters/day, $p<0.001$) were noted. Unlike Duffey *et al* who found that increasing age was a predictor for post-operative hyperoxaluria ⁽¹⁰⁾, this group found that presence of pre-operative stones was the only predictor of hyperoxaluria ⁽¹⁴⁾. Overall, across all three studies, RYGB increased CaOx SS three-four fold compared to patients' baseline studies, with over 80% of all patients having with CaOx SS > 2.

Although most are retrospective or performed primarily in stone formers (a biased population), the urine profile studies summarized in Table 1 (detailed in Supplemental Table S2) remain important. For example, two studies performed in patients with restrictive-only procedures ^(15, 16) found that, although urine absolute oxalate levels do not reach values observed in RYGB, elevations in post-operative CaOx SS still occur due to decreased urine volume ^(15, 16). This highlights the importance of hydration and urine volumes in all bariatric stone formers, regardless of procedure type. Interventional diet or dietary supplement studies in the post-bariatric surgery setting have also provided insights into the mechanisms involved in recurrent stone disease. Pang *et al* (2012, Supplemental Table S2) looked at the effect changing diet in a small number of recurrent stone formers who were, on average, 11 years beyond the procedure RYGB ($n=6$), jejunioileal bypass ($n=2$) or BPD ($n=1$) ⁽¹⁷⁾. The authors performed baseline 24 hour urines on these patients on uncontrolled diets and then placed them on control, metabolic diet consisting of 1000 mg calcium, reduced oxalate (70–80 mg), 20% protein, <25% fat, and 3000 mg sodium diet. They found that, although urine oxalate levels remained high, the metabolic diet positively affected urinary CaOx SS by increasing urine volume and raising urine pH and urinary citrate ⁽¹⁷⁾. Although not supported by their data but perhaps beneficial, the authors recommended additional strategies to reduce oxalate, such as oral calcium supplements and lower fat meals to reduce future stone risk.

These recommendations were further investigated by Froeder *et al* (2012, Supplemental Table S2), who observed similar decreases in urine citrate and total urinary volume in RYGB and BPD patients compared to morbidly obese controls ⁽¹⁸⁾. Interesting, they found that bariatric patients had similar rates of hyperoxaluria (~13–20%) compared to controls at baseline. However, when group of patients ($n=43$) were given a 375 mg oxalate load (spinach juice), bariatric patients had a two-fold elevation in urinary oxalate at all urine time-points compared to controls, suggesting that excessive oxalate absorption was occurring ⁽¹⁸⁾. The authors then tested a subset of these patients ($n=21$) for *Oxalobacter formigines* (a commensal pathogen in the GI tract that uses oxalate as an energy source) colonization and found no difference in rates, again suggesting that the differences in hyperoxaluria between these two populations was due to oxalate over-absorption, not lack of bacterial oxalate consumption. Lastly, Sakhaee and colleagues published two recent 2-phase, placebo crossover studies evaluating the short-term effect of effervescent potassium citrate

and calcium citrate (40 meq potassium, 800 mg calcium, 100 meq citrate/day) in 24 patients at a mean 4.7 years after RYGB⁽¹⁹⁾ and in 15 patients at a mean 4.2 years after RYGB⁽²⁰⁾. From a bone standpoint, the more soluble delivery of calcium lowered markers of bone resorption but had no effect on serum parathyroid hormone⁽¹⁹⁾. The potassium and citrate raised urine pH and lowered calcium oxalate agglomeration by direct crystal testing. Additionally, this product had more pronounced effects on acute serum calcium (measured hourly x 6 hours) after ingestion compared to calcium citrate, suggesting superior calcium uptake and availability⁽²⁰⁾. Although this product is not commercially available, these two placebo-based, interventional trials convincingly contend that calcium citrate reduces stone risk in bariatric stone formers and may be a more suitable supplement than the standard calcium citrate.

KIDNEY STONE INCIDENCE AFTER BARIATRIC SURGERY

The 8 studies that describe kidney stone incidence following bariatric surgery of any type are summarized in Table 1 and listed in Supplemental Table S3. RYGB patients with previous stone history were found to have kidney stone recurrence rate as high as 16.7% within 2 years of RYGB compared to 8.4% of patients with no previous stone history. This finding is limited, however, as only two small series (total n = 102) have reported rates of *recurrent* stone disease following RYGB^(14, 21). Restrictive procedures and obese controls reported stone incidence rates from 1.3 – 4.7% respectively during a similar 2 year time-frame.

Durrani *et al* (2006) was the first to report an increased stone prevalence (3.2% de-novo stones, mean of 2.8 years) in a cohort of 972 RYGB patients compared to rates derived from a control population⁽²¹⁾. Concordantly, Matalga *et al* (2009) reported claims data in a case-control study of 4,639 patients post-RYGB surgery compared to obese controls, determining a 2-fold difference in stone incidence of 7.65% in RYGB versus 4.63% in controls⁽²²⁾. Compared to restrictive procedures (such as the gastric band) which yield an estimated person-time stone incidence rate of 3.40 stones per 1000 person-years⁽²⁵⁾, Matlaga *et al* estimated person-time stone incidence rate of 16.62 stones per 1000 person-years for RYGB and 11.3 stones per 1000 person-years for routine obesity⁽²²⁾. To see if this stone risk phenomenon remained true in non-obese patients, Shimizu *et al* (2012) reviewed CT scans from gastric cancer patients who had either distal gastrectomy with Bilroth I/Roux-en-Y versus total gastrectomy with Roux-en-Y reconstruction⁽²³⁾. In this population, patients with total gastrectomy were more likely to have renal stones by CT diagnosis (21/85, i.e. 25%) than patients with some portion of the stomach remaining (10/141, i.e. 7%). Although urinary chemistries were not reported, the authors hypothesized that total gastrectomy may lead to more fat malabsorption than partial gastrectomy, perhaps exacerbating hyperoxaluria. Furthermore, these authors did not find a significant difference in stone incidence between distal gastrectomy patients with either Bilroth I or Roux-en-Y reconstruction, again suggesting that extent of stomach resection may be more significant than the length of the common channel from an absorptive standpoint. This study, however, does not address potential confounders such as fluid intake differences.

In a large, prospective case series (n=151) of laparoscopic RYGB patients, Valezi (2013) reported de novo stone incidence of 8% one year post-procedure⁽¹⁴⁾. Using multivariate analysis, post-operative hyperoxaluria (OR 1.41, 95% CI 1.101 – 1.803; p=0.006) and hyperuricosuria (OR 1.009, 95% CI 1.002 – 1.016; p=0.013) were found to be the only predictors of developing RYGB-related kidney stones. Although these epidemiological studies are not perfect, it appears that RYGB procedure clearly increases future stone risk at least 2–3 fold, primarily driven by hyperoxaluria. More long-term studies are needed to identify other risks, such as food preference changes (increased leafy green foods) or increased animal protein (potentially leading to higher uric acid intake) in order to solidify mechanisms behind these fluctuations. Additionally, developing a predictive stone risk calculator would help both urologists and bariatric surgeons counsel patients considering RYGB or even screen for metabolic abnormalities in patients who are in the post-operative setting, especially since stone risk in this population appears to increase with time⁽¹⁰⁾.

For restrictive procedures, Semins *et al* (2009) reported through claims data that morbidly obese controls experienced higher incidence of stone disease (6%) over 2½ years than a population of patients after LAGB (1.5%; Table 1, supplemental Table 3)⁽²⁴⁾. This study was the first to suggest that restrictive weight-loss surgeries may minimize urinary metabolic changes compared to malabsorptive procedures. Likewise, Chen *et al* (2013) reported 1% stone incidence rate by chart review of over 400 LAGB (mean 43 months post-op) and SG (mean 27 months post-op) patients, estimating person-time stone incidence rate of 3.40 stones per 1000 person-years for LAGB and 5.25 stones per 1000 person-years for SG⁽²⁵⁾. This contrasts the study by Matalga⁽²²⁾ which estimated person-time stone incidence rate of 16.62 stones per 1000 person-years for RYGB and 11.3 stones per 1000 person-years for routine obesity⁽²²⁾. Based on this epidemiologic data, restrictive bariatric procedures appear to have limited impact on stone risk. More long-term studies are needed to define the nature of the reduced gastric reservoir that may potentially limit fluid intake, reduce urine volume, and increase CaOx SS and stone risk⁽²⁴⁾ as well as the influence of previous kidney stone history on stone recurrence following restrictive bariatric procedures.

PATHOPHYSIOLOGY AND EXPERIMENTAL MODELS OF BARIATRIC SURGERY

To date, clinical data suggest that malabsorptive bariatric procedures have higher incident kidney stone risk through changes in urinary volume, oxalate, and citrate. These procedures, therefore, fall into the spectrum of gastrointestinal disorders characterized by malabsorption of bile salts and/or fatty acids – termed “enteric hyperoxaluria.” In humans, the dicarboxylic anion oxalate is the end product of liver glyoxylate and ascorbic acid metabolism and is a commonly absorbed plant product found in most diets. Mechanistically, as fat is malabsorbed, fat-soluble vitamins and calcium ions are saponified by intraluminal free fatty acids, leading to steatorrhea with subsequent nutrient loss (Figure 1). As a consequence of this reduced calcium availability in the intestinal lumen, there is decreased calcium-oxalate binding and increased free oxalate within the small and large intestine. This increased free oxalate load, otherwise destined for fecal excretion, has a higher chance of either passive or active gut absorption. Once absorbed, the majority of oxalate must be eliminated through the

kidney and, under predisposing conditions, may precipitate with urinary calcium to form insoluble mineral complexes and eventually kidney stones^(11, 18, 26, 27). Concurrently, permeability of the GI tract to oxalate can be dramatically increased by exposure to unconjugated bile salts and long chain fatty acids, both of which have been shown to be increased in the GI tract of RYGB patients^(11, 17, 28–30). In addition to oxalate absorption, significant amounts of fluid and bicarbonate could potentially be lost through the GI tract, especially if the bariatric patient is experiencing diarrhea. Unfortunately, only a small number of human studies have reported rates of malabsorption correlating to urinary oxalate with limited results^(11, 18, 31). In an attempt to better understand these mechanisms, our group established a diet-induced obese rodent model of RYGB surgery and tested the effect of altered dietary fat and oxalate on fecal fat excretion and 24 hour urine parameters⁽³²⁾.

In a cohort of 19 experimental animals and 16 sham-operated controls, we tested two different diets (40% versus 10% fat) with moderate (1.5%) or no oxalate-added content. As expected, no changes in urinary oxalate or fecal fat occurred on these regimens in age-matched, sham-operated control animals⁽³²⁾. However, RYGB animals on high fat and moderate oxalate diets had 8-fold higher fecal fat excretion and heavier, more watery stools, a 5-fold increase in urine oxalate excretion, and 4-fold increase in calculated oxalate supersaturation. Fat malabsorption following RYGB in rats was also recently verified by Stemmer *et al*⁽³³⁾, and although this group did not report urinary oxalate levels, the findings from both studies suggest that fat malabsorption may occur more frequently than what is currently described in the human clinical literature. In experimental RYGB rats in our lab, simply lowering dietary fat resulted in a 40% decrease in oxalate excretion. Interestingly, RYGB animals on a “no-oxalate supplemented” diet had consistently higher urinary oxalate levels than controls, suggesting that, in addition to dietary fat and oxalate, other mechanisms may be responsible for a portion of excessive oxalate excretion (Figure 1).

INTESTINAL COLONIZATION STUDIES USING PROBIOTICS

The lack of the anaerobic bacterium *Oxalobacter formigenes*, a gut commensal capable of using oxalate as an energy source, has been implicated as a potential etiology of hyperoxaluria in calcium oxalate stone formers (i.e. lack of colonization theoretically correlates with higher free luminal oxalate and therefore enhanced oxalate absorption)⁽³⁴⁾. In 2005, subjects, including 6 RYGB patients, with fat malabsorption, hyperoxaluria, and calcium oxalate stones caused by a variety of GI diseases were given the probiotic “Oxadrop®” (*Lactobacillus acidophilus* and *brevis*, *Streptococcus*, and *Bifidobacterium*)⁽³⁵⁾. Over a period of 3 months, mean urinary oxalate levels decreased by 20% in these patients with fairly resistant hyperoxaluria⁽³⁵⁾. This encouraging trial was followed by several encouraging case series showing reductions in urinary oxalate excretion in primary hyperoxaluria (PH) patients administered viable *Oxalobacter* cells⁽⁵⁵⁾. However, a recent multi-center randomized trial of orally administered *O. formigenes* in PH patients, a rare genetic disease characterized by abnormally high hepatic oxalate synthesis and high urinary oxalate excretion, showed no difference in urinary oxalate levels between treated and untreated groups⁽³⁶⁾. Because higher rates of *O. formigenes* colonization has been shown in animal studies to reduce urine levels by alterations in intestinal oxalate handling, it has been suggested that this therapy may be potentially successful in RYGB patients^(12, 18).

To date, no studies have been published on the effect of *O. formigenes* colonization in the RYGB population.

We performed a pilot study (n=4) to evaluate the efficacy of orally administered *O. formigenes* in the RYGB Sprague-Dawley rat model established in our laboratory (Table 2). All animals were studied ~10 weeks post-RYGB procedure and were maintained on either 40% or 10% fat content diets supplemented with 1.5% potassium oxalate (Table 2). The protocol for *Oxalobacter* colonization has been outlined previously ⁽³⁹⁾, and we confirmed lack of colonization in all experimental animals prior to oral gavage with *Oxalobacter*. Mean urinary oxalate excretion prior to oral gavage with *Oxalobacter* was 18.6 +/- 5.7 μ moles/24 hr (Table 2).

After this and following momentary anesthesia using isoflurane inhalation, rats were colonized with an actively growing, 24-hour pure culture of a wild rat strain of *Oxalobacter formigenes* (OXWR) (35 mg of wet weight) by esophageal gavage. After 48 hours, the rats were similarly inoculated a second time. Fresh fecal specimens were collected 7 days after the second gavage for detection of *Oxalobacter*, which was routinely determined by an anaerobic culture method ⁽³⁹⁾. Briefly, ~20 mg of freshly collected fecal material were inoculated into anaerobically sealed vials containing a 20 mM oxalate medium, and after incubation at 37°C for 6–7 days, loss of oxalate in the medium indicates rat colonization status ⁽³⁸⁾. Over an 8 week course, urinary oxalate levels fell more than 70% by manipulations in dietary fat and colonization with *Oxalobacter*, with the lowest post-gavage measurement 4.5 +/- 3.1 μ moles/24 hr, occurring 7 weeks after colonization (G+49, see Table 2). Further studies with additional animal numbers are currently underway in our laboratory. However, based on this promising study, we feel that *O. formigenes* may offer a future potential therapy for RYGB patients who suffer from hyperoxaluria and symptomatic recurrent oxalate stones that is resistant to traditional therapies.

INTESTINAL OXALATE TRANSPORT AND THE SLC26 GENE FAMILY

Studies addressing the mechanisms of intestinal oxalate handling *in vivo* have shown that oxalate is derived from both dietary and endogenous (liver metabolism) sources. Although oxalate is primarily excreted by the kidneys, *adaptive* enteric oxalate elimination can occur under certain conditions ⁽³⁷⁾. In the setting of normal renal function, the kidney excretes ~94% of total body oxalate with a minority of oxalate actively excreted into the intestinal lumen ⁽³⁷⁾. In contrast, when renal function is compromised, as much as 50% of the oxalate load can be excreted enterically (primarily by the distal colon), as demonstrated in 5/6 nephrectomized rats ⁽³⁷⁾. More recent studies in mice and rats have shown that the presence of *Oxalobacter formigenes* within the small and large intestinal lumen can actually promote active oxalate secretion and excretion, not just simply oxalate degradation, resulting in reductions in both plasma and urinary oxalate levels ^(38–40).

Several members of the SLC26 (solute-linked carrier) gene superfamily-encoding anion transport proteins have measurable affinity for the oxalate anion and are expressed along the intestinal tract ⁽⁴¹⁾. Since gastric bypass patients have alterations in oxalate transport (likely due to paracellular permeability changes of oxalate across the large intestine), it is possible

that expression or activity of the oxalate transport proteins are altered within the re-configured RYGB segments of the intestine. Anion transporter SLC26A3 is reported to be responsible for active oxalate uptake, and this transport protein is relatively more abundantly expressed on the apical surface of the large intestine compared to the small intestine (Figure 1)⁽⁴²⁾. Another multifunctional transporter anion-exchanger, PAT1 (SLC26a6), mediates apical oxalate efflux across the mouse small intestine and results in hyperoxaluria in PAT 1 knock out mice⁽⁴³⁾. SLC26A1, or SAT1, is located on the basolateral aspect of human small intestine and colon (Figure 1) and is presumed to be responsible for efflux across the basolateral membrane of the enterocyte⁽⁴¹⁾. To our knowledge, no studies of these transporters have been conducted in bariatric patients., and although speculative, it is possible that alterations in expression or in abundance of these anion transporters could markedly affect oxalate homeostasis in RYGB patients.

MEASURES THAT MAY REDUCE STONE RISK IN BARIATRIC STONE FORMERS

Besides hyperoxaluria, the other commonly cited urinary abnormalities in bariatric surgical patients include low urinary volume and low urine citrate, both of which can significantly increase calcium oxalate risk and supersaturation^(10–12, 44–47). Citrate is the dissociated anion of citric acid, a weak acid that is ingested in dietary fruits and vegetables and is produced endogenously in the tricarboxylic acid cycle. Acid-base status plays the most significant role in citrate excretion, as acidosis will lead to increased mitochondrial citrate utilization. Lower intracellular citrate then facilitates renal citrate reabsorption and decreased urinary citrate excretion. Assuming a 2 liter urine output with normal urine pH and serum potassium, the “optimal” level of urinary citrate excretion is 640 mg/d in healthy individuals, while hypocitraturia is defined as citrate excretion of less than 320 mg per day⁽⁵⁴⁾. Although the literature is scant regarding blood pH in human RYGB patients, both our group and Abegg *et al* have noted metabolic acidosis following experimental RYGB surgery^(32, 48). Taken together with the benefit of potassium calcium citrate in this population (previously described), the current literature suggests that chronic metabolic acidosis may play a larger role in hypocitraturia and stone disease than previously expected. Therefore, replacing citrate in the form of calcium citrate may not only bind oxalate enterically (Table 3) but may also increase urinary citrate, further reducing CaOx stone risk.

Pyridoxal phosphate, the metabolically active form of vitamin B6, is an important co-factor for the transamination reaction of glyoxylate to glycine. When patients are vitamin B6 deficient, the pathway is shunted to oxalate production instead of glycine, resulting in excessive urinary oxalate⁽⁴⁹⁾. Interestingly, a recent retrospective series of over 400 gastric bypass patients demonstrated that almost 20% of these patients were vitamin B6 deficient at one and two years post-surgery⁽⁵⁰⁾. Although these patients did not have corresponding urine oxalate levels to determine causality, it seems reasonable to presume that B6 deficiency could lead to increased liver oxalogenesis, hyperoxaluria, and calcium oxalate stone disease (Figure 1). More studies are needed in this area, especially since a retrospective study of empiric vitamin B6 supplementation in addition to dietary counselling

in patients with idiopathic hyperoxaluria noted an approximately 30% decrease in urine oxalate on follow-up 24-hour urine studies ⁽⁵¹⁾.

Overall, the major strategies to prevent stones after bariatric surgery are similar to those recommended to all stone formers and are summarized in Table 3. They include increased daily fluid intake to achieve urine volumes higher than 2 liters/day and low oxalate (<100 mg/day) intake. Additionally, low sodium and animal protein intake, like that of the Dietary Approaches to Stop Hypertension (DASH)-style diet (high fruit and vegetables, moderate dairy, low animal protein), may encourage favorable dietary patterns and impart a more balanced approach instead of food “avoidance.” (Table 3) The use of calcium sparing diuretics or xanthine oxidase inhibitors should only be prescribed in cases of hypercalciuria or hyperuricosuria, both of which remain fairly rare in the post-bariatric setting. Additionally, bariatric stone formers should reduce daily fat intake to minimize enteric oxalate absorption and consider calcium supplementation using calcium citrate instead of calcium carbonate. Citrate salts, like potassium citrate, may be used to correct metabolic acidosis and hypocitraturia ^(10, 22, 23, 47). As reviewed earlier, probiotics and pyridoxine supplementation may be beneficial, although data are limited ⁽³⁵⁾. Future directions for study or therapy in these patients include a more critical appraisal of bile acid binders (such as cholestyramine) as well as clarification of the role of gut hormones in renal and GI oxalate transport. Since food preference is known to change after bariatric surgery, observational studies evaluating dietary sources of oxalate, such as food frequency questionnaires centering on oxalate-containing foods, may yield additional dietary insights.

CONCLUSION

Based on epidemiologic and urine chemistry data, restrictive bariatric procedures appear to lower urine volume but have limited impact on stone risk. More studies, particularly in patients with previous stone history who undergo a restrictive procedure, are needed to better define the long-term effect of reduced gastric reservoir on stone risk. Roux-en-Y gastric bypass surgery and calcium oxalate stone disease, however, appear to be irrevocably linked through mechanisms of hyperoxaluria, low urine volume, and hypocitraturia. In light of growing obesity and bariatric surgery trends, the development of kidney stones should not be used as a reason to eliminate RYGB from surgical weight loss options. Instead, urologists, nephrologists, dieticians, and bariatric professionals should work together to design human and experimental investigations that more clearly explain the etiologies of each of these findings and best means of modifying kidney stone risk in this population of patients well on their way to a longer and healthier lifestyle.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schema of hyperoxaluria mechanisms following Roux-en-Y gastric bypass surgery.

Proposed mechanisms fall into three categories: gut transporter changes, gut environment changes, and nutritional effects. All pathways ultimately lead to hyperoxaluria by increasing active or passive oxalate absorption, oxalogenesis, and/or decreasing active oxalate secretion in the GI tract. Gut transporter changes, specifically Slc26A3 and A6, are speculative due to lack of human studies and absence of highly sensitive and specific Slc26 antibodies in gut and kidney. Although gut environment changes and vitamin B6 nutritional effects have been shown in a variety of different animal studies, they are also speculative since the data have not been specifically generated in relation to RYGB and oxalate. With strong historical and recent experimental human and animal data, increased intestinal oxalate permeability as a consequence of fat malabsorption remains the most likely pathway for increased free intestinal oxalate, oxalate absorption, and hyperoxaluria.

Table 1

Summary of mean 24-hour urine data* and kidney stone incidence from obese controls, RYGB, or restrictive procedures stratified by stone history

RYGB and 24 Hour Urine (~12 Month F/U)	Patient Number	Mean Urinary Oxalate	Mean Urinary Citrate	Mean Urinary Volume
Non-stone formers, prospective ^(8, 10-14)	277	Pre-op = 28 mg/day Post-op = 44 mg/day	Pre-op = 737 mg/day Post-op = 442 mg/day	Pre-op = 1.6 L/day Post-op = 1.1 L/day
Non-stone formers, retrospective ^(7, 15,16,18,45,46)	177	54 mg/day	312 mg/day	1.1 L/day
Primarily stone formers, any type ^(17, 44, 47)	166	71 mg/day	415 mg/day	1.4 L/day
LAGB or SG and 24 Hour Urine				
Non-stone formers, retrospective ^(15, 16)	30	36 mg/day	NR	1.3L/day

Procedure, Stone History (~2 year F/U)	Kidney Stone Incidence
RYGB, stone history ^(14, 21, 52)	17/102 = 16.7%
RYGB, no stone history ^(14, 21, 22, 52)	509/5955 = 8.5%
LAGB/SG, no stone history ^(24, 25)	8/618 = 1.3%
Obese controls, no stone history ^(22,24)	227/4840 = 4.7%

Key:

* Mean values calculated using weighted averages from multiple studies; F/U – follow-up; RYGB - Roux-en-Y gastric bypass; NR – not recorded; LAGB – laparoscopic adjustable gastric band; SG – sleeve gastrectomy; primary data can be found in Supplemental data Tables S1–3

Table 2

Pre- and post-OXWR gavage urinary oxalate and creatinine levels in rats 10 weeks post-RYGB on 40% or 10% fat diets supplemented with 1.5% potassium oxalate

Gavage w/OXWR (n=4 RYGB rats)	Urinary Oxalate $\mu\text{moles}/24 \text{ hr}$	Urinary Creatinine $\mu\text{moles}/24 \text{ hr}$	Diet	Number colonized
Pre-gavage	18.6 ± 5.7	159.1 ± 8.3	40% Fat	0
G+7	16.3 ± 3.7	155.3 ± 7.1	40% Fat	4
G+14	17.3 ± 2.4	155.2 ± 9.1	40% Fat	4
G+21	13.7 ± 2.8	155.6 ± 6.5	40% Fat	4
G+28	12.4 ± 1.4	163.4 ± 9.3	40% Fat	4
G+42	5.9 ± 0.5	147.7 ± 12.7	10% Fat	4
G+49	4.5 ± 0.9	145.6 ± 5.8	10% Fat	4
G+56	5.0 ± 0.6	152.6 ± 6.2	10% Fat	4

Key: OxWR - *Oxalobacter formigenes* wild rat strain; G – gavage + time in days

Table 3

Strategies, limitations, and solutions to reduce calcium oxalate stone risk following RYGB

Strategy	Limitations	Solutions
Urine output > 2 liters/day	Compliance, small stomach pouch	Push fluids high in citrate (i.e. lemonade), downloadable phone application reminders
Low fat diet (<25% daily calories)	High prevalence of fatty foods	Early satiety after surgery, patient education
Low oxalate diet (<80–100 mg/day) for hyperoxaluria	Component in vegetables and “healthy” foods (peanuts, bran, soy), bioavailability variable	Patient education *, downloadable phone applications, “balance” versus avoidance
Low salt (<2300 mg/day) and animal protein (0.8 – 1.0 gm/kg/day) intake	Both ubiquitous, particularly in American diet	Patient education, follow Dietary Approaches to Stop Hypertension (DASH)-style diet
Potassium citrate for hypocitraturia	Tolerability, absorption efficacy, expense	Dispense as liquid or crystal/powder forms
Calcium citrate and dietary calcium to bind enteric oxalate	Tolerability, absorption efficacy, compliance, expense	Patient education, low dose chewable citracal (250 mg) taken 5–6x daily with small meals
Probiotics for hyperoxaluria	No commercially available <i>Oxalobacter</i> , unknown efficacy of <i>Lactobacillus sp.</i>	Most yogurts contain protein, calcium, and forms of probiotics
Vitamin B6 (pyridoxine) for hyperoxaluria	Well studied in primary hyperoxaluria; potential for neurotoxicity at high doses	Consider supplementing 50 mg/day (low dose) x 6 months then discontinue

Key:

* Very high and high oxalate content foods can be found at: <https://regepi.bwh.harvard.edu/health/Oxalate/files>