Published in final edited form as:

J Urol. 2009 January ; 181(1): 161–166. doi:10.1016/j.juro.2008.09.028.

Prevalence of Hyperoxaluria After Bariatric Surgery

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Abstract

Purpose—Recent investigations have shown increased oxalate excretion in patients in whom kidney stones formed after contemporary bariatric surgery. We determined whether there is an increased prevalence of hyperoxaluria after such procedures performed in nonstone formers.

Materials and Methods—A total of 58 nonstone forming adults who underwent laparoscopic Roux-en-Y (52) or a biliopancreatic diversion-duodenal switch procedure (6) collected 24-hour urine specimens 6 months or greater after bariatric surgery. Standard stone risk parameters were assessed. Comparisons were made with a group of healthy nonstone forming adults and stone formers in a commercial database.

Results—The bariatric group had a significantly higher mean urinary oxalate excretion compared to that in controls and stone formers (67.2 vs 34.1 and 37.0 mg per day, respectively, $p < 0.001$). Mean oxalate excretion of patients who underwent a biliopancreatic diversion-duodenal switch procedure was higher than in the Roux-en-Y group (90 vs 62 mg per day, $p < 0.05$). There was a significant correlation between urine oxalate excretion on the 2 collection days but some patients showed significant variability. Of the patients 74% showed hyperoxaluria in at least 1, 24-hour urine collection and 26% demonstrated profound hyperoxaluria, defined as oxalate excretion more than 100 mg per day, in at least 1 collection. This occurred in 3 of the 6 patients in the biliopancreatic diversion-duodenal switch group and in 12 of the 52 in the Roux-en-Y cohort. Hyperoxaluria was not uniformly expressed.

Conclusions—There is a high prevalence of hyperoxaluria in patients without a history of kidney stones who undergo bariatric surgery. A significant proportion of these patients have profound hyperoxaluria, which is not uniformly expressed.

Keywords

kidney; kidney calculi; hyperoxaluria; bariatric surgery; obesity

The prevalence of obesity in the United States is now 33%.¹ Studies have shown that obesity is associated with increased mortality, diabetes, heart failure, hypertension, obstructive sleep apnea, coronary artery disease and stroke.² These negative outcomes have prompted many individuals to attempt to lose weight using various methods. The initial management approach is based on lifestyle changes, including exercise and diet. While they are successful in some

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^{*}Financial interest and/or other relationship with Litholink/Lablore.

[‡]Financial interest and/or other relationship with Med Reviews Urology, Altus Pharmaceutical and Alita Pharmaceutical.

Study obtained approval from the Wake Forest University School of Medicine, Winston-Salem, North Carolina and Clarian/Methodist Hospital, Indianapolis, Indiana institutional review boards.

individuals, many do not lose weight or only have a partial or transient response. Pharmacological treatments aimed at decreasing fat absorption have also been used in this patient population.

Laparoscopic bariatric surgery provides a minimally invasive surgical option. This is a popular option in this population, as evidenced by greater than 100,000 of these procedures performed per year in the United States.³ These patients have experienced several benefits, including significant weight reduction, reversal of insulin resistance, improvement in hypertension and other cardiovascular risks, and decreased mortality.⁴

Potential complications are associated with this procedure, including renal morbidity. There are reports of patients in whom kidney stones develop after bariatric surgery and metabolic testing has demonstrated that they may have profound hyperoxaluria.^{5,6} In fact, renal failure due to oxalate nephropathy has been reported.⁷ Sinha et al observed that hyperoxaluria may be prevalent in nonstone formers who undergo to RY for weight loss.⁶ However, this was based on only a small number of patients. They also analyzed a larger number of stone formers and suggested that hyperoxaluria appears to develop at least 6 months after the operation. We determined the prevalence and degree of hyperoxaluria in nonstone forming adults at least 6 months after a bariatric procedure.

METHODS

Approval for this study was obtained from the institutional review boards of Wake Forest University School of Medicine, Winston-Salem, North Carolina and Clarian/Methodist Hospital, Indianapolis, Indiana. Patients were recruited by urological research coordinators who periodically attended the bariatric clinics at the 2 institutions. All patients who were competent, English speaking adults were asked to participate in the study. Only those without a history of nephrolithiasis were recruited. Patients provided informed consent for participation. They had undergone laparoscopic 100 or 150 cm RY or a DS procedure. Of the patients 56 collected 2, 24-hour urine specimens while consuming a self-selected diet and 2 provided only a single urine collection. General dietary recommendations in these patients included the consumption of 1.2 to 1.5 gm protein per kg of ideal body weight, no more than 15 gm carbohydrate per meal with 4 to 6 meals daily and 1,200 mg calcium citrate with vitamin D supplementation daily. The parameters measured were calcium, citrate, creatinine, magnesium, sodium, ammonium, oxalate, phosphorous, pH, sulfate, uric acid, urea and volume. Urine supersaturation of calcium oxalate, calcium phosphate and uric acid were calculated using Equil II.

Urinary parameters in patients with bariatric surgery were compared to those in normal, nonstone forming adults and in 1,303 patients with kidney stones from the Litholink database. Mean age $\pm$ SD in this cohort was 49.2 ± 14.6 years, 58% were male and 43% were female. Patients with cystinuria, bowel disease, bariatric surgery and hyperparathyroidism were excluded from study. Stone composition in this cohort was not known but we believe that most participants were probably calcium stone formers. The normal cohort consisted of 168 nonstone forming adults 18 to 78 years old, of whom 57% were male and 43% were female, who collected 1, 24-hour urine specimen.

Relationships between the various urinary parameters, and patient and surgical characteristics were examined. ANOVA with the post hoc Scheffe test was used to compare urine chemistry findings in the 3 groups using creatinine excretion, gender and body weight at urine collection as covariates. Similarly ANOVA with a post hoc test using gender and weight as covariates was performed to compare creatinine among the groups. The Bonferroni correction was used for multiple comparisons. ANOVA with the post hoc test was also used to compare oxalate

excretion by procedure type using creatinine excretion, gender and body weight at urine collection as covariates. Data from ANOVA are presented as the least squares mean $\pm$ SEM. A general linear model was used to determine correlations among oxalate excretion, weight and other urine parameters. All statistical tests were 2-sided with statistical significance considered at $\alpha = 0.05$.

RESULTS

A total of 58 nonstone forming patients, including 52 with RY and 6 with DS, participated in the study after undergoing bariatric surgery. There were 51 females and 7 males with a mean age of 45.3 years (range 23 to 63). Preoperatively mean BMI $\pm$ SD was 51.9 ± 9.0 kg/m². In the RY and DS groups mean BMI was 51.8 ± 8.9 and 52.7 ± 10.6 kg/m², respectively. The overall mean decrease in BMI was 35.2% with a mean reduction of 35.0% and 36.7% in the RY and DS groups, respectively. Urine specimens were collected a mean of 427 ± 261 days after surgery (range 188 to 1,441).

The table lists urinary parameters in patients with bariatric surgery, routine stone formers and normal participants. These data were obtained from ANOVA, using which all comparisons were corrected for age, gender and creatinine excretion. The bariatric cohort had a urine oxalate excretion that was significantly higher than that of stone formers and normal participants. When analyzed by type of surgery, patients who had undergone DS had significantly higher urine oxalate excretion than patients with RY (90.0 ± 12.8 vs 61.9 ± 4.3 mg per day, $p < 0.05$, fig. 1). There was no correlation of urine oxalate excretion with the time between bariatric surgery and urine collection (fig. 2, A). In patients who completed 2, 24-hour urine collections there was a highly significant correlation of urine oxalate excretion on each day ($r = 0.77$, $p < 0.001$, fig. 2, B). There was 25% variability in oxalate excretion between 2 consecutive 24-hour urine collection in 20% of stone formers and 50% variability in 6% of this cohort.

There was significant variation in oxalate excretion in some study participants. Of 58 patients 43 (74%) demonstrated hyperoxaluria (oxalate excretion more than 45 mg per day) on at least 1 collection, while only 29 of 56 (52%) demonstrated this degree of oxalate excretion during the 2 collections. Of 58 patients 15 (26%) showed profound hyperoxaluria (oxalate excretion more than 100 mg per day) on at least 1 collection, while only 5 of 56 (9%) showed this on each collection. This occurred in 3 of the 6 patients (50%) in the DS group and in 12 of the 52 (23%) in the RY cohort (not significantly different, $\alpha > 0.1$). It was present in each collection in 2 patients in the DS group and in 3 in the other cohort.

Analysis of other urine chemistry results revealed that ammonium and magnesium excretion was significantly higher in patients with bariatric surgery compared to that in normal participants and stone forming patients (table 1). Urine calcium excretion was lowest in bariatric cases but it only attained statistical significance compared to stone forming cases. Uric acid excretion was lower in bariatric than in stone forming cases and urine volume was higher in bariatric than in normal cases. Citrate and pH, which are critical determinants of stone risk, were not different among the groups. Creatinine was significantly lower in the bariatric group than in the normal cohort ($1,551.7 \pm 47.4$ vs $1,669.1 \pm 25.0$ mg, $p = 0.026$). However, values in the latter group did not differ from those in stone formers ($1,608 \pm 9.8$ mg, $p = 0.299$).

Using a general linear model to determine which urine chemistry results correlated with urine oxalate excretion we found that urine sodium and volume positively correlated with oxalate excretion (each $p < 0.01$). Urine calcium excretion negatively correlated with urine oxalate excretion ($p = 0.025$). There was no association of urine oxalate with age, gender, BMI, the decrease in BMI and time from surgery.

DISCUSSION

This study demonstrates that there is a high prevalence of hyperoxaluria in individuals without a history of nephrolithiasis who have undergone RY or DS. This has been previously demonstrated in stone forming patients by Asplin and Coe,⁵ and most recently by Sinha et al.⁶ The latter group also reported this occurrence in 5 of 8 nonstone formers (62.5%) 12 months after RY. However, the degree of hyperoxaluria and the variability of expression were not defined. Our findings demonstrate that a significant number of patients without a history of nephrolithiasis have profound hyperoxaluria (more than 100 mg per day), which places them not only at risk for nephrolithiasis, but also for oxalate induced nephropathy.⁷

To our knowledge the reasons for the high prevalence of hyperoxaluria in these individuals have not been defined. The hyperoxaluria associated with jejunoileal bypass was hypothesized to be enteric in origin and provoked by fat malabsorption, the binding of oxalate to cations such as calcium, and fatty acid and bile salt stimulation of gut oxalate transport, each of which increases intestinal oxalate absorption and oxalate excretion.⁸ Fat malabsorption could have had a significant role in our patients who underwent DS. Puzziferri et al reported that fat absorption was 19% higher after DS and 67% higher after RY.⁹ The lower oxalate excretion after RY relative to DS could be due to this discrepancy. However, a number of patients in the RY group also had profound hyperoxaluria and, thus, other mechanisms warrant consideration. A progressive rise in gut peptide YY has been reported during the first 6 months after RY.¹⁰ Peptide YY increases gastrointestinal transit time and, thus, increases absorption time. This suggests that the gut is functionally adapting during this 6-month interval.¹⁰ Sinha et al provided indirect evidence that hyperoxaluria develops 6 months after RY, supporting a time relation to gut adaptation.⁶ Other changes in gastrointestinal physiology may be influential. Increased colonic oxalate absorption promoted by bile salts was also proposed to have a role in hyperoxaluria after jejunoileal bypass.⁸ The decreased amount of small bowel exposed to bile salts after RY could increase the delivery of these substances to the colon and facilitate oxalate absorption.

Dietary factors may also influence hyperoxaluria in the post-bariatric surgical setting. The amount of oxalate and calcium consumed and the ratio of these substances in the diet influences oxalate excretion. Of interest is that the negative correlation of urine calcium with urine oxalate that we found in the bariatric group may reflect a lower dietary calcium intake in those with the highest urine oxalate. While these patients were instructed to consume calcium citrate and vitamin D supplements, and adhere to dietary recommendation, compliance data on diet and supplement intake were not captured. Thus, noncompliance with these recommendations may have influenced this association. It is also possible that malabsorption of calcium and vitamin D could have been responsible for this correlation. Fat consumption may also have an impact. Dietary fat mainly consists of triglycerides, which are hydrolyzed by pancreatic lipases into diglycerides, monoglycerides, fatty acids and glycerol. Certain fatty acids promote paracellular transport and could facilitate oxalate transport in the gut.¹¹ Thus, the amount and type of fat consumed may be important factors.

Other potential changes warrant consideration. Endogenous oxalate synthesis could increase. Alterations in the fecal microenvironment could influence oxalate excretion. These patients are typically administered antibiotics in the perioperative period. This could eliminate oxalate degrading bacteria in the colon, such as *Oxalobacter formigenes*. The degradation of oxalate in the gut decreases the pool available for absorption. This has been hypothesized to be a mechanisms for hyperoxaluria in patients with cystic fibrosis, a group in which antibiotics are frequently prescribed.¹² In addition, it was demonstrated in an in vitro model that this bacterium or its lysate stimulates oxalate secretion in the gut.¹³ Therefore, its absence could theoretically increase oxalate excretion by decreasing secretion, which would increase the

delivery of oxalate to the kidney.¹³ The influence of oxalate degrading bacteria on urinary oxalate excretion in individuals who undergo bariatric surgery was previously suggested by Allison et al.¹⁴ They reported that feces from patients with jejunoileal bypass degrade oxalate less efficiently than those of normal individuals and hypothesized that this may result in increased absorption of dietary oxalate in the former cohort, causing hyperoxaluria.

In addition to oxalate excretion, there were other differences among the bariatric surgery, normal and stone forming groups. Calcium excretion in stone formers and normal participants was higher, which could have been due to malabsorption in the bypass group or to other factors. High urine magnesium excretion in the bariatric group could have been due to diet or possibly to calcium malabsorption. Ammonium excretion in the bypass group was higher. A potential explanation is the gastrointestinal loss of bicarbonate due to the altered gastrointestinal properties that develops in some of these patients, which results in acidosis and increased ammonium excretion. However, we would have expected urine citrate to decrease if acidosis was significant. The increased sodium excretion in the bypass group could have been due to increased dietary sodium consumption. The lower calcium phosphate supersaturation in the bypass group was due to the higher volume and lower calcium excretion.

While we believe that the high prevalence and degree of hyperoxaluria in our study was due to bariatric surgery, this could not be proved because preoperative oxalate excretion was not determined. This is a weakness of our study. However, others have measured oxalate excretion in morbidly obese patients and mean excretion was much lower at between 29 and 41 mg.^{6, 15,16}

Hyperoxaluria places patients at risk for renal morbidity. It is a risk factor for stone formation. There are limited data on the prevalence of nephrolithiasis after contemporary bariatric surgery. Durrani et al noted an 8.8% stone prevalence before RY in a cohort of 972 patients.¹⁷ A recurrent stone developed in 31% of this cohort a mean of 1.9 years after surgery. Moreover, the first stone developed in 3.5% of cases a mean of 2.8 years postoperatively. Marceau et al reported that the prevalence of nephrolithiasis was 6.3% before DS, which increased to 14.8% 15 years later.¹⁸ Nelson et al reported that 11% of patients who underwent long limb RY had the first kidney stone at a mean followup of 4 years.¹⁹ In addition, hyperoxaluria may result in oxalate nephropathy.⁷ This group of patients may be more susceptible to the latter because renal biopsies in morbidly obese patients with normal renal function before bariatric surgery have revealed glomerular pathology.²⁰

CONCLUSIONS

The overall health benefits of contemporary bariatric surgery at this time outweigh the attendant side effects. It is anticipated that more bariatric surgery will be performed as the obesity epidemic in this country accelerates. The high prevalence of hyperoxaluria and the potential for renal morbidity suggest that studies of renal function and stone formation with time should be done in this cohort. The mechanisms of hyperoxaluria must be elucidated, so that optimum treatments can be developed if an increase in stone risk and renal dysfunction is noted in this cohort. In addition, similar studies in patients undergoing other bariatric procedures, such as gastric banding, are warranted to determine whether there is such a high prevalence of hyperoxaluria.

Acknowledgements

Sue Ann Backus, Shelley Handa and Susan Donohue assisted with the study.

Abbreviations and Acronyms

BMI

body mass index

DS

biliopancreatic-duodenal switch procedure

RY

Roux-en-Y gastric bypass

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Figure 1.

Urine oxalate excretion by group. *A*, oxalate excretion in patients with bariatric surgery, routine stone formers and nonstone forming participants. Asterisks indicate $p < 0.001$ vs bariatric surgery. *B*, oxalate excretion in patients with RY (*RYGB*) and those with DS. Data are shown as least mean square using ANOVA with creatinine, gender and weight included in model as covariates. Asterisk indicates $p < 0.001$ vs RY.

Figure 2.

Urine oxalate variation. *A*, average urine oxalate excretion for 2 collections did not correlate with time since bariatric surgery. Solid line indicates linear regression ($r = 0.00$, $p = \text{not significant}$). *B*, oxalate excretion on urine collection days 1 and 2. Dashed line indicates linear regression ($r = 0.77$, $p < 0.001$). Solid line indicates line of identity. *d*, day.

	Mean $\pm$ SEM Bariatric	Mean $\pm$ SEM Normal	Mean $\pm$ SEM Stone Former
Vol (ml)	2.07 $\pm$ 0.1	1.43 $\pm$ 0.05 [*]	1.81 $\pm$ 0.02
Oxalate (mg)	67.2 $\pm$ 1.9	34.1 $\pm$ 1.1 [*]	37.0 $\pm$ 0.4 [*]
Calcium (mg)	140.3 $\pm$ 14.3	164.2 $\pm$ 7.7	216.4 $\pm$ 2.9 [*]
Citrate (mg)	620.8 $\pm$ 39.7	572.1 $\pm$ 24.1	547.4 $\pm$ 8.2
Uric acid (mmol)	0.62 $\pm$ 0.02	0.63 $\pm$ 0.01	0.70 $\pm$ 0.004 [*]
Urine pH	6.02 $\pm$ 0.06	5.97 $\pm$ 0.04	6.01 $\pm$ 0.01
Ammonium (mmol)	50.5 $\pm$ 1.8	31.2 $\pm$ 1.7 [*]	34.0 $\pm$ 0.4 [*]
Sodium (mmol)	194.2 $\pm$ 8.0	163.2 $\pm$ 4.2 [†]	186.4 $\pm$ 1.6
Potassium (mmol)	57.5 $\pm$ 2.8	62.2 $\pm$ 1.5	59.1 $\pm$ 0.6
Phosphorous (gm)	0.95 $\pm$ 0.03	0.89 $\pm$ 0.02	1.02 $\pm$ 0.01
Magnesium (mg)	130.0 $\pm$ 4.7	99.0 $\pm$ 2.6 [*]	100.4 $\pm$ 1.0 [*]
Sulfate (mmol)	41.02 $\pm$ 1.7	47.89 $\pm$ 1.5 [†]	40.84 $\pm$ 0.3
Supersaturation:			
Calcium oxalate	7.78 $\pm$ 0.58	7.41 $\pm$ 0.35	7.34 $\pm$ 0.12
Calcium phosphate	0.66 $\pm$ 0.14	1.30 $\pm$ 0.09 [†]	1.36 $\pm$ 0.03 [*]
Uric acid	0.95 $\pm$ 0.13	1.30 $\pm$ 0.08	1.20 $\pm$ 0.03

^{*}
p < 0.001.

[†]
p < 0.05.