Response to Dietary Oxalate after Bariatric Surgery

Leila Froeder, Carlos Haruo Arasaki,* Carlos Alberto Malheiros,† Alessandra Calábria Baxmann,* and Ita Pfeferman Heilberg**

Summary

Background and objectives Bariatric surgery (BS) may be associated with increased oxalate excretion and a higher risk of nephrolithiasis. This study aimed to investigate urinary abnormalities and responses to an acute oxalate load as an indirect assessment of the intestinal absorption of oxalate in this population.

Design, setting, participants, & measurements Twenty-four–hour urine specimens were collected from 61 patients a median of 48 months after BS (post-BS) as well as from 30 morbidly obese (MO) participants; dietary information was obtained through 24-hour food recalls. An oral oxalate load test (OLT), consisting of 2-hour urine samples after overnight fasting and 2, 4, and 6 hours after consuming 375 mg of oxalate (spinach juice), was performed on 21 MO and 22 post-BS patients 12 months after BS. Ten post-BS patients also underwent OLT before surgery (pre-BS).

Results There was a higher percentage of low urinary volume (<1.5 L/d) in post-BS versus MO ($P<0.001$). Hypocitraturia and hyperoxaluria ($P=0.13$ and $P=0.36$, respectively) were more frequent in BS versus MO patients. The OLT showed intragroup ($P<0.001$ for all periods versus baseline) and intergroup differences ($P<0.001$ for post-BS versus MO; $P=0.03$for post-BS versus pre-BS). The total mean increment in oxaluria after 6 hours of load, expressed as area under the curve, was higher in both post-BS versus MO and in post-BS versus pre-BS participants ($P<0.001$ for both).

Conclusions The mean oxaluric response to an oxalate load is markedly elevated in post-bariatric surgery patients, suggesting that increased intestinal absorption of dietary oxalate is a predisposing mechanism for enteric hyperoxaluria.

Clin J Am Soc Nephrol 7: 2033–2040, 2012. doi: 10.2215/CJN.02560312

*Nephrology Division, Federal University of São Paulo, São Paulo, Brazil; and †Surgery Division, Santa Casa Medical School, São Paulo, Brazil

Correspondence: Dr. Ita Pfeferman Heilberg, Nephrology Division, Federal University of São Paulo, Rua Botucatu, 740, Vila Clementino, São Paulo, SP, Brazil 04023-900. Email: ipheilberg@nefro.epm.br

Introduction

Nephrolithiasis has emerged as a potential outcome after bariatric surgery (BS) (1,2), occurring in up to 7.6% of bariatric patients in a 5-year period, which represents almost a two-fold increased risk compared with obese controls (3). Several recent studies demonstrated that urinary abnormalities, such as low urine volume, hypocitraturia, and more commonly, hyperoxaluria, may predispose bariatric patients to nephrolithiasis (4–12). Hyperoxaluria is the most frequent lithogenic factor detected in the majority of studies, with prevalence rates between 29% and 74% (4–12) and time to onset of 3–24 months after the procedure (8,9). The potential underlying mechanisms for hyperoxaluria have not yet been determined, but some degree of fat malabsorption is speculated to play a role through the binding of fatty acids to calcium, thereby inhibiting the formation of poorly soluble, nonabsorbable calcium oxalate in the intestinal lumen (11,13). Similarly, less calcium in the intestinal lumen as a result of lower dietary calcium intake after surgery (2,14,15) may also reduce these poorly soluble compounds, resulting in more free oxalate available for absorption and thereby increasing urinary oxalate. Increased net intestinal absorption of oxalate due to dysfunction of the anion exchanger SLC26A6, which acts as an oxalate secretor in the small bowel (16), warrants investigation. Finally, alterations in the intestinal bacterial flora (17) after BS with a lower intestinal colonization by *Oxalobacter formigenes* (18,19), an oxalate-degrading bacterium, could lead to a reduction in oxalate secretion in bariatric patients if present.

The aim of this study was to investigate urinary abnormalities and responses to an acute oxalate load as an indirect assessment of the net intestinal absorption of oxalate in patients who underwent BS.

Materials and Methods

Study Participants

Patients who had undergone BS a minimum of 6 months prior were recruited between September 2007 and December 2010 from the Department of Surgery of the Federal University of São Paulo and from the Santa Casa Medical School. A total of 61 post-BS patients were enrolled, with a median time of 48 months from the procedure (interquartile range [IQR], 12–84 months), including 58 patients with standard Roux-en-Y gastric bypass (RYGB) and 3 patients with biliopancreatic diversion with duodenal switch (BD-DS). Bariatric patients were compared with a group of 30

morbidly obese (MO) patients with a body mass index (BMI) ≥40 kg/m^2 scheduled to undergo bariatric surgery due to the presence of obesity comorbidities. Exclusion criteria comprised patients with age <18 years, estimated 24-hour GFR <60 ml/min per 1.73 m^2, hyperkalemia, pregnancy, inflammatory bowel disease, and treatment with glucocorticoids. Written consent was obtained from all participants, and the local Ethics Committee of the Federal University of São Paulo approved this study.

Study Protocol

Urinary and Serum Parameters and Nutritional Assessment. All participants were requested to provide 24-hour urine specimens while maintaining a self-selected diet reported through a 24-hour food recall (20). In addition, morning fasting blood samples were obtained, and body weight and height were measured to calculate BMI. Multivitamins, diuretics, and calcium supplements were to be discontinued at least 72 hours before urine collections. Low urinary volume was defined as <1500 ml/d, hypercalciuria as urinary calcium ≥250 or 300 mg/24 h (for women and men, respectively), hyperuricosuria as uric acid ≥750 or 800 mg/24 h (for women and men, respectively), hypocitraturia as citrate <320 mg/24-hour, hyperoxaluria as urine oxalate >45 mg/24 h, and hypomagnesuria as urinary magnesium <70 mg/24 h.

Oxalate Load Test. Of the 61 post-BS and 30 MO participants, 22 and 21 patients were submitted to an oxalate load test (OLT), respectively. Patients who had been submitted to BD-DS surgery and/or presented kidney stones were not recruited for the OLT. Only patients who accepted to continue on the study protocol, because of the time availability to stay in the laboratory for an additional period of 8 hours, were selected for the OLT. The modified OLT, adapted from a previously described methodology (21), consisted of urine specimens obtained after overnight fasting and 2, 4, and 6 hours after the consumption of a dietary source of oxalate (spinach juice) containing 375 mg of oxalate. A subgroup of 10 post-BS patients underwent OLT both at 6 months after surgery and immediately before surgery (pre-BS). The oxaluric response was assessed at each 2-hour period and also as the total increment after 6 hours, expressed as area under the curve (AUC).

***O. formigenes* Colonization.** A subgroup of 10 post-BS patients and 13 MO participants provided stool samples for the determination of *O. formigenes* colonization status. Genomic DNA from the stool specimen was extracted using the Qiagen QIAamp DNA stool kit and amplified as described elsewhere (22).

Urinary oxalate was measured by an enzymatic method using a kit provided by Trinity Biotech. Calcium and magnesium were determined by a colorimetric method, uric acid was measured by an uricase method, sodium and potassium were determined by ion-selective electrodes, and citrate was measured by an enzymatic assay using citrate lyase. Creatinine was determined by an isotope dilution mass spectrometry traceable method (23) and urea was determined by an enzymatic method. Urinary pH was measured with a pH electrode. The ion-activity product with respect to calcium oxalate, SSCaOx (Tiselius index), was calculated (24). Serum parathyroid hormone (PTH) was determined by immunofluorometric assay for the intact molecule, and albumin was estimated by the bromocresol green albumin method. Nutrient intake was calculated with a computer program developed in our department, with food tables from the US Department of Agriculture. Oxalate intake was calculated based on the table from Holmes (25). For better accuracy, sodium chloride (NaCl) was estimated from 24-hour sodium urine excretion. Protein intake was also estimated by the protein equivalent of nitrogen appearance (PNA) formula using adjusted body weight as described elsewhere (26).

Statistical Analyses

Chi-squared or Fisher exact tests were used to compare the percentage of metabolic disturbances between groups. All other parameters were submitted to a normality test and because most of them did not present a normal curve distribution, nonparametric tests (Mann–Whitney) were performed. The Spearman correlation coefficient was used for association between the PNA and uric acid excretion. Accordingly, variables were expressed as the median with the IQR. With respect to the results of the OLT, we used ANOVA for repeated measures, complemented with a profile contrast test and Tukey test in order to evaluate the interaction effects of surgery versus oxalate load factors (27). For this purpose, variables were converted into ranks. The only exception was represented by the values of AUC, with a normal distribution, hence being compared by unpaired *t* test. All statistical tests were performed at a significance level of $P<0.05$. The statistical analysis was performed with the SAS software for Windows 8.02.

Results

Demographics

There were a greater number of women in both the post-BS and MO groups, with 51 women and 10 men versus 24 women and 6 men, respectively. The median age of post-BS patients did not differ from MO participants at 47 years (IQR, 39–55) versus 49 years (IQR, 45–55), respectively ($P=0.63$). The overall mean decrease in BMI after surgery was 36%. The median BMI of the post-BS patients, was significantly lower than MO participants at 31 kg/m^2 (IQR, 26–35) versus 43 kg/m^2 (IQR, 41–49), respectively ($P<0.001$). Six of the 61 post-BS patients reported having passed stones before the bypass procedure. Five post-BS patients who reported previously passing a kidney stone after their enrollment in the study were submitted to unenhanced helical tomography, which revealed the presence of stones. Two of these patients also had reported previously passing kidney stones. One of participants from the MO group also had a history of nephrolithiasis.

Biochemical Characteristics

Urine and Serum Profile. Table 1 shows the results for the urinary and serum biochemical parameters of each group. Median urinary volume, calcium, uric acid, urea, and creatinine were significantly lower and the median urinary magnesium was significantly higher in post-BS patients compared with MO participants. Median urinary oxalate, citrate, SSCaOx (Tiselius index), and pH did not

Table 1. Median values of urinary and serum parameters

Parameter	MO (*n*=30)	Post-BS (*n*=61)	*P*
Urine			
Volume (ml/d)	1593 (1100–2100)	1140 (910–1460)	0.002
Calcium (mg/d)	161 (23–488)	89 (21–270)	<0.001
Oxalate (mg/d)	29 (22–42)	26 (22–37)	0.39
Citrate (mg/d)	522 (362–830)	472 (307–814)	0.40
Magnesium (mg/d)	77 (53–106)	91 (77–139)	0.01
Uric acid (mg/d)	711 (564–815)	401 (345–504)	<0.001
Sodium (mEq/d)	184 (122–252)	141 (105–181)	0.01
Creatinine (mg/d)	1424 (1092–1637)	1035 (907–1222)	<0.001
Urea (g/d)	17 (15–25)	14 (10–17)	0.003
pH	5.81 (5.31–6.17)	5.78 (5.49–6.33)	0.37
Tiselius index (SSCaOx)	0.92 (0.71–1.52)	0.74 (0.47–1.30)	0.23
Serum			
Creatinine (mg/dl)	0.72 (0.60–0-85)	0.69 (0.62–0.76)	0.72
Uric acid (mg/dl)	5.5 (3.1–11.1)	4.3 (2.2–9.1)	0.002
Albumin (mg/dl)	4.2 (4.1–4.4)	4.2 (4.0–4.3)	0.29
Potassium (mEq/L)	4.3 (4.0–4.5)	4.2 (4.0–4.4)	0.49
Ionized calcium (mmol/L)	1.27 (1.25–1.29)	1.25 (1.23–1.28)	0.85
Parathyroid hormone (pg/ml)	58 (43–72)	56 (44–69)	0.46
HCO_3 (mEq/L)	27 (26–30)	28 (26–31)	0.47

Data are presented as median (interquartile range). MO, morbidly obese; BS, bariatric surgery.

differ between groups. There has been no statistical difference in urinary oxalate between RYGB patients (*n*=58) and BD-DS patients (*n*=3) at 26 mg/24 h (IQR, 22–37) versus 28 mg/24 h (IQR, 22–49), respectively (*P*=0.66; data not shown). Except for the median serum uric acid levels, which were significantly lower in post-BS patients than in MO patients, we observed that serum parameters such as creatinine, albumin, potassium, ionized calcium, PTH, and bicarbonate did not differ significantly between groups. One of the post-BS patients who passed stones before the procedure presented hypercalcemia at the initial serum determination and was further diagnosed as having primary hyperparathyroidism. The percentage of metabolic disturbances in both groups is presented in Table 2. The percentage of patients with a urinary volume <1.5 L/d was significantly higher and the percentages of hypercalciuria, hypomagnesuria, and hyperuricosuria were significantly lower in post-BS patients compared with MO participants. Hypocitraturia and hyperoxaluria were more frequent in the post-BS group compared with the MO group at 34% versus 17% (*P*=0.13) and 20% versus 13% (*P*=0.36), respectively. Individual values for urinary oxalate and citrate for each group are presented in Figure 1. One of the post-BS patients found to be hyperoxaluric had passed stones before the surgery, which then recurred after the surgery. This patient was not submitted to further OLT. Of the four remaining patients who formed stones after enrollment, one was hypocitraturic, one was hypomagnesuric, and two presented low urinary volume.

Table 2. Distribution of metabolic disturbances

	MO (*n*=30)	Post-BS (*n*=61)	*P*
Hypocitraturia	5 (17)	21 (34)	0.13
Hyperoxaluria	4 (13)	12 (20)	0.36
Hypomagnesuria	13 (43)	10 (16)	0.02
Hyperuricosuria	14 (47)	3 (5)	<0.001
Hypercalciuria	5 (17)	1 (2)	<0.001
Urinary volume <1.5 L	11 (37)	50 (82)	<0.001

Data are presented as *n* (%). MO, morbidly obese; BS, bariatric surgery.

Nutritional Profile. The estimated nutrient intake is shown in Table 3. Energy, carbohydrate, protein, PNA (corrected for body weight), and NaCl intake were significantly lower for post-BS patients compared with MO participants. Calcium intake was not significantly different between groups and median oxalate intake was lower in post-BS versus MO patients at 126 mg/d (IQR, 15–398) versus 166 mg/d (IQR, 24–425), respectively (*P*=0.07). PNA (g/d) was directly correlated with uric acid excretion in both post-BS (*r*=0.43; *P*<0.001) and MO (*r*=0.63; *P*<0.001) patients (data not shown).

Oral OLT. Median sex and age distribution did not differ between post-BS versus MO patients submitted to the test (19 women and 3 men versus 17 women and 4 men; median age 53 years [IQR, 47–55] versus 50 years [IQR, 40–55], respectively). The post-BS patients presented significantly lower median BMI than the MO patients (31 kg/m^2 [IQR, 26–33] versus 43 kg/m^2 [IQR, 41–48]) and a median time of 12 months from the procedure (IQR, 6–60 months). Significant intragroup differences were observed in the median urinary oxalate/creatinine ratio (uOx/uCr) for all periods after the oxalate load versus baseline in both post-BS and MO patients (*P*<0.001) (Figure 2A) and also intergroup differences in post-BS versus MO patients (*P*<0.001). In addition, a significant effect of the interaction

of surgery versus oxalate load factors ($P<0.001$) was observed. The total mean AUC for the 6-hour period demonstrated a higher oxalate excretion in post-BS patients versus MO participants ($P<0.001$) (Figure 2B). When the patients were classified as hyperoxaluric in both the post-BS ($n=5$) and MO groups ($n=4$) based on their 24-hour oxalate excretion, as shown in Figure 3, significant differences were observed in median uOx/uCr for all periods after the oxalate load compared with the baseline ($P<0.001$) and between post-BS and MO patients ($P<0.001$). In addition, post-BS patients always presented a higher uOx/uCr compared with MO patients, irrespective of whether they presented hyperoxaluria in their 24-hour urine samples ($P<0.001$), indicating that the bariatric surgery *per se* (and not the oxalate load), was the factor predisposing to a higher oxaluria. Figure 4 shows the results of the subgroup of 10 post-BS patients (9 women and 1 man), aged 48 years (IQR, 47–51), who also underwent the OLT before the procedure. After BS, they presented significantly lower BMI than before BS (29 kg/m^2 [IQR, <26–34] versus 43 kg/m^2 [IQR, 40–48]). Significant intragroup ($P<0.001$) and intergroup (post-BS versus pre-BS; $P=0.03$) median uOx/uCr were observed at all periods after load, and the interaction effects of surgery versus oxalate load factors were also significant ($P=0.01$) (Figure 4A). The total mean AUC for the 6-hour period demonstrated a higher oxalate excretion in post-BS versus pre-BS ($P<0.001$) (Figure 4B).

***O. formigenes* Colonization.** *O. formigenes* was present in 4 of 10 post-BS patients (40%) and in 2 of 13 MO participants (15%), with no significant differences between them (data not shown).

Discussion

This study demonstrated that hyperoxaluria and hypocitraturia were common abnormalities after BS but that their rates were not significantly different from those detected in the MO group. However, bariatric patients presented an exaggerated urinary response to the oral oxalate load compared with MO participants and compared with their own results before surgery.

The majority of post-BS patients presented low urinary volume as a predominant lithogenic factor, most likely related to low fluid intake due to a small gastric pouch, as also reported by others (7,8,11). The 24-hour urinary pH did not differ between groups. Hypocitraturia is not a uniform finding after BS (5,6,8,10,11). This study detected

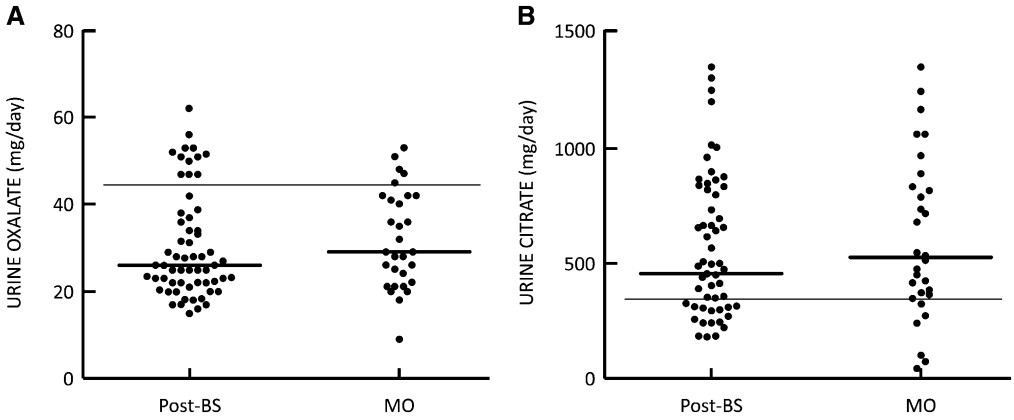

Figure 1. | **Individual values for daily excretion of urinary oxalate and citrate.** 24-hour urine oxalate (A) and citrate (B) in both groups of patients. Horizontal bolded bars indicate median values. Solid lines indicate reference limits. BS, bariatric surgery; MO, morbidly obese.

Table 3. Nutritional data

	MO ($n=30$)	Post-BS ($n=61$)	P
Energy (kcal/d)	1739 (1182–2743)	1272 (931–1714)	0.01
Lipid (g/d)	45 (27–57)	53 (32–76)	0.27
Carbohydrate (g/d)	199 (149–390)	142 (106–192)	<0.001
Protein (g/d)	75 (62–100)	51 (39–70)	<0.001
Protein (g/kg per day)	1.13 (0.82–1.46)	0.78 (0.58–1.25)	0.01
PNA (g/kg per day)	1.04 (0.79–1.37)	0.80 (0.63–0.99)	0.002
Oxalate (mg/d)	166 (24–425)	126 (15–398)	0.07
Calcium (mg/d)	502 (395–1278)	517 (324–740)	0.32
NaCl (g/d)	11 (7–15)	8 (6–11)	0.01

Data are presented as median (interquartile range). MO, morbidly obese; BS, bariatric surgery; PNA, protein equivalent of nitrogen appearance.

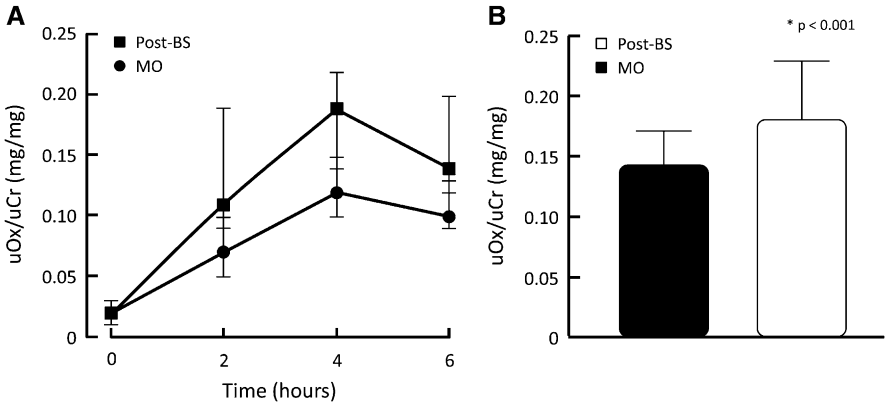

Figure 2. | Oxalate load test in post-BS and MO patients. (A) Significant intragroup differences of uOx/uCr in all periods of the oxalate load test versus baseline ($P<0.001$) and intergroup differences (post-BS versus MO; $P<0.001$) at all periods after load were observed and the interaction effect of "surgery" versus "oxalate load" factors was also significant ($P<0.001$). Values are median and error bars represent 25th and 75th percentiles. (B) The mean values of area under the curve for the 6-hour period of the test for both groups. uOx/uCr, urinary oxalate/creatinine ratio; BS, bariatric surgery; MO, morbidly obese.

hypocitraturia in 34% of patients, which is similar to that reported by Park *et al.* (7) (31%) but is lower than other studies that reported prevalence rates from 44% to 63% (9,12,28). The reasons for hypocitraturia after BS in these studies have not been fully elucidated. In the current series, metabolic acidosis can be ruled out because of the normal levels of serum bicarbonate detected in these patients. It is also possible that the low protein intake, and hence lower acid ash content, found in this group of post-BS patients may have contributed to preventing a greater reduction in urinary citrate (29). In accordance with other reports (5–12,30), hypercalciuria was not a frequent finding in this sample of post-BS patients. The lack of hypercalciuria may be ascribed to low protein, calcium, and salt intake, which is usually found in this population (14,15,31,32) and was detected in our patient cohort as well. It may also have occurred because calcium supplements were withdrawn 3 days before urine collection in our study. Hypomagnesuria was not frequent in our series of post-BS patients, which was also the case in several other studies (5,7,9–12). This is most likely because magnesium depletion is more commonly due to diarrhea, which was detected in only two post-BS patients (one RYGB and one BD-DS). These latter patients did present low urinary magnesium. The very low prevalence of hyperuricosuria after BS (5%) is in agreement with the findings of other authors (7) who observed similar rates of hyperuricosuria after BS (2%). This finding might have been a consequence of the low protein intake evidenced by low PNA and its direct correlation with urinary uric acid in BS patients. Moreover, the lower serum uric acid observed in BS patients may be related to the correction of hyperinsulinemia after BS (33,34).

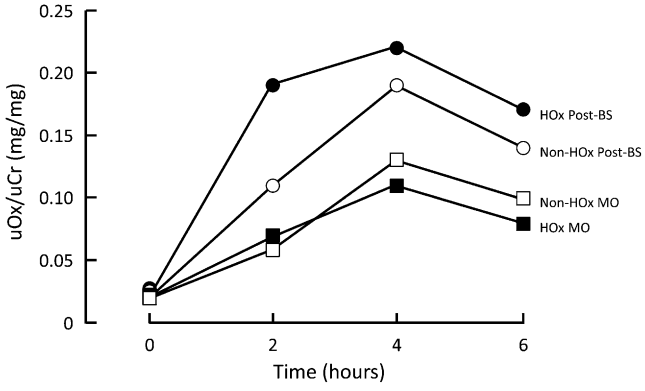

Figure 3. | Median urinary oxalate-to-creatinine ratio during the oxalate load test in either hyperoxaluric or non-hyperoxaluric post-BS and MO patients. Significant intragroup ($P<0.001$) and intergroup (post-BS versus MO; $P<0.001$) differences at all periods after load. Interaction effect of "surgery" versus "oxalate load" was also significant ($P<0.001$). uOx/uCr, urinary oxalate/creatinine ratio; HOx, hyperoxaluric; BS, bariatric surgery; MO, morbidly obese.

The prevalence rate of hyperoxaluria after BS (20%) in our study agrees closely with the rate reported by Duffey *et al.* (8) (29%), but was lower than the rates reported by other studies, which reached values as high as 74% (5,9–12). On the other hand, the current mean oxalate excretion values were similar to those reported by other investigators (7,8,11). The highly variable degree of secondary hyperoxaluria may be due to differences in protein, lipid, calcium, and oxalate intake from other studies. However, only a handful of studies have reported dietary patterns (8,9,11,35). The present pattern of low protein intake by post-BS patients, evidenced by the food recalls and the lower urea, uric acid, and creatinine excretion, may have interfered with our rates of hyperoxaluria (36,37). The observed decrease in creatinine excretion was not only secondary to lower protein intake but was also most likely due to weight loss and decreased muscle mass (38). In addition, the usual low calcium and oxalate intake determined in this study may have also been responsible for the lower percentages of hyperoxaluria (39–41). Although the absolute lipid content in the typical diets of post-BS patients did not differ from that of the MO participants, the percentage of fat calculated from the total energy value was 37%, which far exceeds the upper limit of 30% suggested by the US dietary reference intakes. As previously

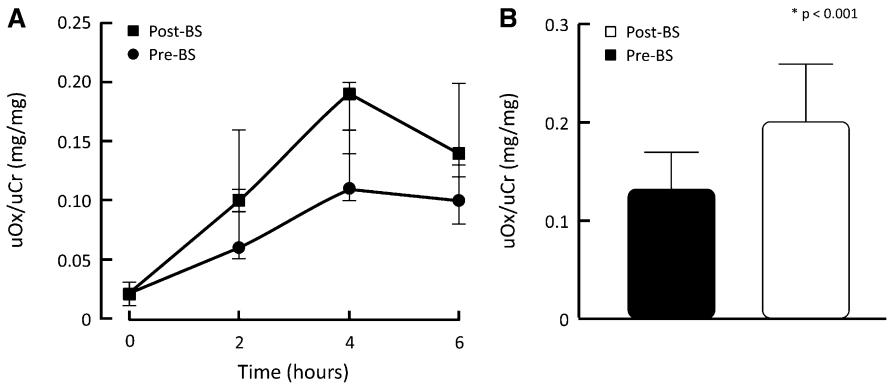

Figure 4. | **Oxalate load test before and after BS (n=10)**. (A) Significant intragroup differences of uOx/uCr in all periods of the oxalate load test versus baseline ($P<0.001$) and intergroup differences (post-BS versus pre-BS; $P=0.03$) at all periods after load were observed and the interaction effect of "surgery" versus "oxalate load" factors was also significant ($P=0.01$). Values are median and error bars represent 25th and 75th percentiles. (B) The mean values of area under the curve for the 6-hour period of the test performed before and after BS. uOx/uCr, urinary oxalate/creatinine ratio; BS, bariatric surgery.

shown by our group (13), fat malabsorption may act synergically with high oxalate intake to produce elevations in urinary oxalate excretion. Although the contribution of fat malabsorption to increased oxaluria after BS is still under debate (11,35), the additional influence of a high fat content in the diet, as presently disclosed, can further confer a risk for hyperoxaluria. In addition, the lower rates of hyperoxaluria in this series could have been attributed to the lower BMI (42,43) and Roux limb length (44) of our patients compared with other studies (11).

Finally, calcium oxalate supersaturation (Tiselius index) was not significantly different between groups. Although some authors have reported increased SSCaOx (5–8,11), this has not been a uniform finding (9,10,12). It is possible that in this study, the increased supersaturation was negated by lower urine calcium and higher magnesium excretion.

Our most important result is the remarkable increase observed in post-BS patients in oxalate excretion after the dietary oxalate load, which was further corroborated by similar responses obtained in the same patients evaluated both before and after BS. These findings highlight the importance of research into postprandial urinary oxalate excretion peaking 2–4 hours after an oxalate load, as reported elsewhere (37,45). This excretion implies that an oxalate-rich meal is able to induce temporary states of hyperoxaluria after gastric bypass procedures, which may not be detectable in 24-hour urine samples, and highlight the fact that BS *per se* imposed a marked oxaluric response, irrespective of the level of the previous 24-hour urinary oxalate excretion. The fact that the oxalate load in this study was devoid of calcium, protein, and fat and was given under fasting conditions further discriminates the ability of increased dietary oxalate to disclose the presence of intestinal oxalate hyperabsorption under this condition. As recently shown by Bergsland *et al.* (46), urinary oxalate halved in two bariatric stone formers with the administration of a low-oxalate diet if compared to oxalate excretion on a self-selected diet.

Although *O. formigenes* status was determined in a small number of patients in this study, there were no differences in the colonization status between groups, suggesting that the loss of *O. formigenes* colonization is unlikely to be the primary cause of hyperoxaluria after surgery, as argued by other investigators (47). Changes in the activity of other oxalate transporters have not been evaluated in this study.

In the current series, 6 of 61 post-BS patients (9.8%) formed stones preoperatively, with 2 of the 6 patients (one-third) developing recurrent stones postoperatively, and 3 of 61 patients (4.9%) forming stones *de novo* after surgery. The discrimination between increased *de novo* nephrolithiasis or recurrence of stones in participants who were prone to forming them after BS was outside the scope of this study and was also limited due to the small size of the cohort. Nevertheless, these findings suggest that patients with histories of preoperative stones must be screened more closely for postoperative stone formation, as recommended by Durrani *et al.* (48).

One potential limitation in our study refers to the 24-hour food recall, which could have misreported nutrient intake. However, a five-step method (20), developed by the US Department of Agriculture for collecting such recalls, was used to minimize this bias. Although other studies that evaluated urinary parameters after BS have also utilized a single 24-hour urine collection (4–9), we recognize a single collection as a potential limitation in our study because it does not provide information on the within-person variability. Standardizing values of oxalate to urine creatinine during the test were aimed to correct the errors related to fluid intake and state of diuresis. Therefore, nonstandardized oxalate values were not provided because urine volume was not available for analysis. Finally, the small number of feces samples obtained for *O. formigenes* data might have compromised the results about *O. formigenes* colonization.

In conclusion, this study showed that bariatric patients, when challenged by an oxalate load, presented an exaggerated oxaluric response, suggesting that increased intestinal absorption of dietary oxalate is a predisposing mechanism for enteric hyperoxaluria. These data suggest that after BS, patients may benefit from a low-oxalate diet.

Acknowledgments

We thank Larissa Gorayb Ferreira Mota and Silvia Regina Moreira for their technical assistance.

This study was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (Grant 2008/02279-4) and the Conselho Nacional de Desenvolvimento Científico e Tecnológico (Grant 475681/2007-0).

Portions of this study were presented at the Annual Meeting of the American Society of Nephrology, November 16–21, 2010, in Denver, Colorado, and at the World Congress of Nephrology, April 8–12, 2011, in Vancouver, Canada.

Disclosures

None.

References

1. Balsiger BM, Kennedy FP, Abu-Lebdeh HS, Collazo-Clavell M, Jensen MD, O'Brien T, Hensrud DD, Dinneen SF, Thompson GB, Que FG, Williams DE, Clark MM, Grant JE, Frick MS, Mueller RA, Mai JL, Sarr MG: Prospective evaluation of Roux-en-Y gastric bypass as primary operation for medically complicated obesity. *Mayo Clin Proc* 75: 673–680, 2000
2. Mechanick JI, Kushner RF, Sugerman HJ, Gonzalez-Campoy JM, Collazo-Clavell ML, Guven S, Spitz AF, Apovian CM, Livingston EH, Brolin R, Sarwer DB, Anderson WA, Dixon J: American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical Guidelines for Clinical Practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. *Surg Obes Relat Dis* 4[Suppl]: S109–S184, 2008
3. Matlaga BR, Shore AD, Magnuson T, Clark JM, Johns R, Makary MA: Effect of gastric bypass surgery on kidney stone disease. *J Urol* 181: 2573–2577, 2009
4. Nelson WK, Houghton SG, Milliner DS, Lieske JC, Sarr MG: Enteric hyperoxaluria, nephrolithiasis, and oxalate nephropathy: Potentially serious and unappreciated complications of Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 1: 481–485, 2005
5. Sinha MK, Collazo-Clavell ML, Rule A, Milliner DS, Nelson W, Sarr MG, Kumar R, Lieske JC: Hyperoxaluric nephrolithiasis is a complication of Roux-en-Y gastric bypass surgery. *Kidney Int* 72: 100–107, 2007
6. Asplin JR, Coe FL: Hyperoxaluria in kidney stone formers treated with modern bariatric surgery. *J Urol* 177: 565–569, 2007
7. Park AM, Storm DW, Fulmer BR, Still CD, Wood GC, Hartle JE 2nd: A prospective study of risk factors for nephrolithiasis after Roux-en-Y gastric bypass surgery. *J Urol* 182: 2334–2339, 2009
8. Duffey BG, Pedro RN, Makhlouf A, Kriedberg C, Stessman M, Hinck B, Ikramuddin S, Kellogg T, Slusarek B, Monga M: Roux-en-Y gastric bypass is associated with early increased risk factors for development of calcium oxalate nephrolithiasis. *J Am Coll Surg* 206: 1145–1153, 2008
9. Duffey BG, Alanee S, Pedro RN, Hinck B, Kriedberg C, Ikramuddin S, Kellogg T, Stessman M, Moeding A, Monga M: Hyperoxaluria is a long-term consequence of Roux-en-Y gastric bypass: A 2-year prospective longitudinal study. *J Am Coll Surg* 211: 8–15, 2010
10. Patel BN, Passman CM, Fernandez A, Asplin JR, Coe FL, Kim SC, Lingeman JE, Assimos DG: Prevalence of hyperoxaluria after bariatric surgery. *J Urol* 181: 161–166, 2009
11. Kumar R, Lieske JC, Collazo-Clavell ML, Sarr MG, Olson ER, Vrtiska TJ, Bergstralh EJ, Li X: Fat malabsorption and increased intestinal oxalate absorption are common after Roux-en-Y gastric bypass surgery. *Surgery* 149: 654–661, 2011
12. Maalouf NM, Tondapu P, Guth ES, Livingston EH, Sakhaee K: Hypocitraturia and hyperoxaluria after Roux-en-Y gastric bypass surgery. *J Urol* 183: 1026–1030, 2010
13. Ferraz RR, Tiselius HG, Heilberg IP: Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion. *Kidney Int* 66: 676–682, 2004
14. Goode LR, Brolin RE, Chowdhury HA, Shapses SA: Bone and gastric bypass surgery: Effects of dietary calcium and vitamin D. *Obes Res* 12: 40–47, 2004
15. Duran de Campos C, Dalcanale L, Pajecki D, Garrido AB Jr, Halpern A: Calcium intake and metabolic bone disease after eight years of Roux-en-Y gastric bypass. *Obes Surg* 18: 386–390, 2008
16. Freel RW, Hatch M, Green M, Soleimani M: Ileal oxalate absorption and urinary oxalate excretion are enhanced in Slc26a6 null mice. *Am J Physiol Gastrointest Liver Physiol* 290: G719–G728, 2006
17. Li JV, Ashrafian H, Bueter M, Kinross J, Sands C, le Roux CW, Bloom SR, Darzi A, Athanasiou T, Marchesi JR, Nicholson JK, Holmes E: Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. *Gut* 60: 1214–1223, 2011
18. Kaufman DW, Kelly JP, Curhan GC, Anderson TE, Dretler SP, Preminger GM, Cave DR: Oxalobacter formigenes may reduce the risk of calcium oxalate kidney stones. *J Am Soc Nephrol* 19: 1197–1203, 2008
19. Allison MJ, Cook HM, Milne DB, Gallagher S, Clayman RV: Oxalate degradation by gastrointestinal bacteria from humans. *J Nutr* 116: 455–460, 1986
20. Moshfegh AJ, Rhodes DG, Baer DJ, Murayi T, Clemens JC, Rumpler WV, Paul DR, Sebastian RS, Kuczynski KJ, Ingwersen LA, Staples RC, Cleveland LE: The US Department of Agriculture Automated Multiple-Pass Method reduces bias in the collection of energy intakes. *Am J Clin Nutr* 88: 324–332, 2008
21. Krishnamurthy MS, Hruska KA, Chandhoke PS: The urinary response to an oral oxalate load in recurrent calcium stone formers. *J Urol* 169: 2030–2033, 2003
22. Sidhu H, Allison M, Peck AB: Identification and classification of Oxalobacter formigenes strains by using oligonucleotide probes and primers. *J Clin Microbiol* 35: 350–353, 1997
23. Bartels H, Böhmer M, Heierli C: [Serum creatinine determination without protein precipitation]. *Clin Chim Acta* 37: 193–197, 1972
24. Tiselius HG: Aspects on estimation of the risk of calcium oxalate crystallization in urine. *Urol Int* 47: 255–259, 1991
25. Harvard School of Public Health. HSPH Nutrition Department's oxalate documentation. Available at: http://regepi.bwh.harvard.edu/health/Oxalate/files. Accessed September 25, 2008
26. Sargent JA, Gotch FA: Mass balance: A quantitative guide to clinical nutritional therapy. I. The predialysis patient with renal disease. *J Am Diet Assoc* 75: 547–551, 1979
27. Conover WJ, Iman RL: Rank transformations as a bridge between parametric and nonparametric statistics. *Am Stat* 35: 124–129, 1981
28. Penniston KL, Kaplon DM, Gould JC, Nakada SY: Gastric band placement for obesity is not associated with increased urinary risk of urolithiasis compared to bypass. *J Urol* 182: 2340–2346, 2009
29. Knight J, Easter LH, Neiberg R, Assimos DG, Holmes RP: Increased protein intake on controlled oxalate diets does not increase urinary oxalate excretion. *Urol Res* 37: 63–68, 2009
30. Kruseman M, Leimgruber A, Zumbach F, Golay A: Dietary, weight, and psychological changes among patients with obesity, 8 years after gastric bypass. *J Am Diet Assoc* 110: 527–534, 2010
31. Taylor EN, Curhan GC: Oxalate intake and the risk for nephrolithiasis. *J Am Soc Nephrol* 18: 2198–2204, 2007
32. Holmes RP, Goodman HO, Hart LJ, Assimos DG: Relationship of protein intake to urinary oxalate and glycolate excretion. *Kidney Int* 44: 366–372, 1993
33. Puig JG, Martínez MA: Hyperuricemia, gout and the metabolic syndrome. *Curr Opin Rheumatol* 20: 187–191, 2008
34. Tasca A: Metabolic syndrome and bariatric surgery in stone disease etiology. *Curr Opin Urol* 21: 129–133, 2011
35. Odstrcil EA, Martinez JG, Santa Ana CA, Xue B, Schneider RE, Steffer KJ, Porter JL, Asplin J, Kuhn JA, Fordtran JS: The contribution of malabsorption to the reduction in net energy absorption after long-limb Roux-en-Y gastric bypass. *Am J Clin Nutr* 92: 704–713, 2010
36. Giannini S, Nobile M, Sartori L, Dalle Carbonare L, Ciuffreda M, Corrò P, D'Angelo A, Calò L, Crepaldi G: Acute effects of moderate dietary protein restriction in patients with idiopathic hypercalciuria and calcium nephrolithiasis. *Am J Clin Nutr* 69: 267–271, 1999
37. Knight J, Holmes RP, Assimos DG: Intestinal and renal handling of oxalate loads in normal individuals and stone formers. *Urol Res* 35: 111–117, 2007
38. Baxmann AC, Ahmed MS, Marques NC, Menon VB, Pereira AB, Kirsztajn GM, Heilberg IP: Influence of muscle mass and physical

activity on serum and urinary creatinine and serum cystatin C. *Clin J Am Soc Nephrol* 3: 348–354, 2008
39. Siener R, Ebert D, Nicolay C, Hesse A: Dietary risk factors for hyperoxaluria in calcium oxalate stone formers. *Kidney Int* 63: 1037–1043, 2003
40. von Unruh GE, Voss S, Sauerbruch T, Hesse A: Dependence of oxalate absorption on the daily calcium intake. *J Am Soc Nephrol* 15: 1567–1573, 2004
41. Holmes RP, Assimos DG: The impact of dietary oxalate on kidney stone formation. *Urol Res* 32: 311–316, 2004
42. Taylor EN, Curhan GC: Determinants of 24-hour urinary oxalate excretion. *Clin J Am Soc Nephrol* 3: 1453–1460, 2008
43. Taylor EN, Curhan GC: Body size and 24-hour urine composition. *Am J Kidney Dis* 48: 905–915, 2006
44. Nelson WK, Fatima J, Houghton SG, Thompson GB, Kendrick ML, Mai JL, Kennel KA, Sarr MG: The malabsorptive very, very long limb Roux-en-Y gastric bypass for super obesity: Results in 257 patients. *Surgery* 140: 517–522, discussion 522–523, 2006
45. Holmes RP, Ambrosius WT, Assimos DG: Dietary oxalate loads and renal oxalate handling. *J Urol* 174: 943–947, discussion 947, 2005
46. Bergsland KJ, Zisman AL, Asplin JR, Worcester EM, Coe FL: Evidence for net renal tubule oxalate secretion in patients with calcium kidney stones. *Am J Physiol Renal Physiol* 300: F311–F318, 2011
47. Duffey BG, Miyaoka R, Holmes R, Assimos D, Hinck B, Korman E, Kieley F, Ikramuddin S, Kellogg T, Moeding A, Monga M: Oxalobacter colonization in the morbidly obese and correlation with urinary stone risk. *Urology* 78: 531–534, 2011
48. Durrani O, Morrisroe S, Jackman S, Averch T: Analysis of stone disease in morbidly obese patients undergoing gastric bypass surgery. *J Endourol* 20: 749–752, 2006

Received: March 12, 2012 **Accepted:** August 9, 2012

Published online ahead of print. Publication date available at www.cjasn.org.