Stone formation and management after bariatric surgery

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Abstract | Obesity is a significant health concern and is associated with an increased risk of nephrolithiasis, particularly in women. The underlying pathophysiology of stone formation in obese patients is thought to be related to insulin resistance, dietary factors, and a lithogenic urinary profile. Uric acid stones and calcium oxalate stones are common in these patients. Use of surgical procedures for obesity (bariatric surgery) has risen over the past two decades. Although such procedures effectively manage obesity-dependent comorbidities, several large, controlled studies have revealed that modern bariatric surgeries increase the risk of nephrolithiasis by approximately twofold. In patients who have undergone bariatric surgery, fat malabsorption leads to hyperabsorption of oxalate, which is exacerbated by an increased permeability of the gut to oxalate. Patients who have undergone bariatric surgery show characteristic 24 h urine parameters including low urine volume, low urinary pH, hypocitraturia, hyperoxaluria and hyperuricosuria. Prevention of stones with dietary limitation of oxalate and sodium and a high intake of fluids is critical, and calcium supplementation with calcium citrate is typically required. Potassium citrate is valuable for treating the common metabolic derangements as it raises urinary pH, enhances the activity of stone inhibitors, reduces the supersaturation of calcium oxalate, and corrects hypokalaemia. Both pyridoxine and probiotics have been shown in small studies to reduce hyperoxaluria, but further study is necessary to clarify their effects on stone morbidity in the bariatric surgery population.

Tarplin, S. *et al. Nat. Rev. Urol.* **12**, 263–270 (2015); published online 7 April 2015; doi:10.1038/nrurol.2015.67

Introduction

Obesity is an important health problem affecting children, adolescents, and adults worldwide. In the USA alone, it has been estimated that approximately one-third of adults are obese.[1] Surgical procedures for the management of obesity, referred to as bariatric surgeries, have been shown to be effective for weight loss and for reducing the incidence of obesity-related complications such as diabetes and hypertension.[2] Rates of bariatric surgery increased steeply in the USA during the late 1990s, peaking in 2004 at 135,985 procedures per year and plateauing at 124,838 procedures per year in 2008.[3,4]

Weight loss following bariatric surgery is achieved through malabsorption of nutrients, restriction of food intake, or a combination of both. The Roux-en-Y gastric bypass (RYGB; Figure 1) is one such procedure that comprises a combination of restrictive and malabsorptive elements. It involves the creation of a small gastric pouch that limits oral intake, and the reconfiguration of the small intestine leading to mild malabsorption of food. This procedure remains the most commonly performed form of bariatric surgery, accounting for 47% of all such procedures worldwide in 2011.[5] The second most common approach, accounting for 28% of bariatric surgeries performed worldwide, is a sleeve gastrectomy (Figure 2), a restrictive procedure in which a tubular stomach is created following the removal of the greater curvature.[5]

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Competing interests
The authors declare no competing interests.

Among the many long-term complications of bariatric surgery is an increased risk of nephrolithiasis, as initially described in 2005, in a case series of 23 patients who underwent RYGB.[6] Since that time, numerous studies have reported that bariatric surgery increases the incidence of stone formation and alters urinary chemistry profiles.[7–10] This Review summarizes the problems of stone formation in the bariatric surgery population and discusses relevant dietary recommendations, current medical therapies, and new therapeutic directions for the management of urolithiasis in this population.

Epidemiology of stones

Obese individuals

The prevalence of urolithiasis has increased over the past few decades, mirroring the growth in obesity rates. Obese individuals are at an increased risk of urolithiasis compared with people of normal weight. Increased BMI may be associated with increased urinary excretion of calcium, uric acid and oxalate, which contribute to the formation of calcium-containing stones.[11] A long-term, prospective study involving multiple cohorts (the Health Professionals Follow-up Study [$n = 45{,}988$ men aged 40–75 years], the Nurses' Health Study I [$n = 93{,}758$ "older" women aged 34–59 years] and the Nurses' Health Study II [$n = 101{,}877$ "younger" women aged 27–44 years]) revealed that obesity and weight gain were associated with an elevated risk of nephrolithiasis among men and women across different age groups.

Key points

- The propensity for kidney stone formation in patients who have undergone bariatric surgery is well documented and presents a unique treatment challenge
- The pathogenesis of kidney stones in these patients involves the malabsorption of fat, which leads to unbound oxalate being absorbed in excess in the gut
- Specific 24 h urine derangements in the bariatric surgery population include hyperoxaluria, hyperuricosuria, low urine volume and hypocitraturia
- Dietary prevention of stones with a high-fluid diet and limitation of oxalate and sodium is key; calcium supplementation should also be considered
- Potassium citrate is helpful as an alkalinizing agent and promotes activity of stone inhibitors
- Pyridoxine and probiotics require further investigation in this setting

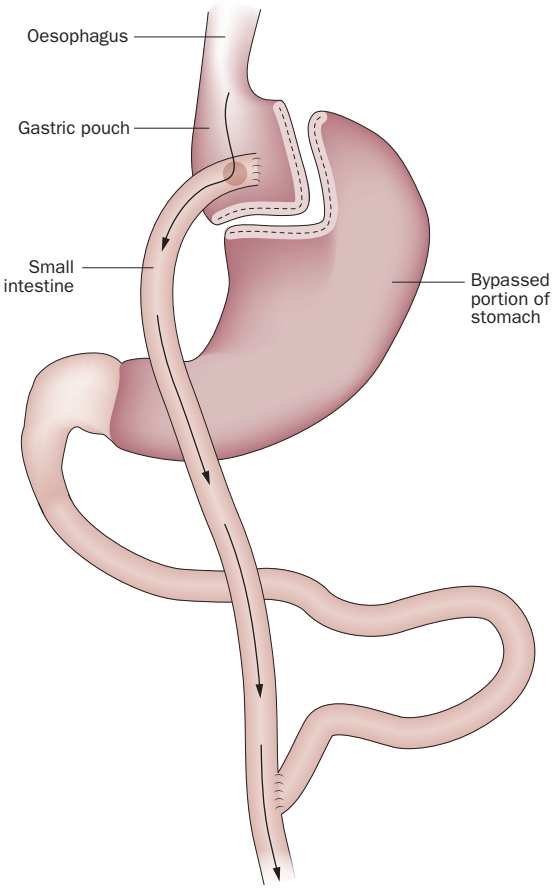

Figure 1 | Roux-en-Y gastric bypass, the most commonly performed bariatric surgery. This procedure comprises a combination of restrictive and malabsorptive elements. It involves the creation of a small gastric pouch that limits oral intake, and the reconfiguration of the small intestine leading to mild malabsorption of food. The arrows show the passage of nutrients.

The researchers found that individuals in a higher weight category (>100.0 kg) experienced an increased relative risk (RR) of stones compared with individuals weighing <68.2 kg, with women experiencing a greater degree of increase compared with men (RR 1.89 for older women and 1.92 for younger women versus 1.44 for men).[11] This finding was consistent even when controlling for potential confounding factors, such as diet, fluid intake, and certain medications.[11] Similarly, women with a BMI >30 kg/m^2 had an approximately twofold increased risk of urolithiasis compared with women with a BMI in the range 21–23 kg/m^2. Although the mechanism for the increased risk of nephrolithiasis in obese patients is not entirely clear, some evidence exists that both insulin resistance and dietary factors are involved.[12]

Metabolic syndrome consists of a constellation of conditions that include obesity, dyslipidaemia, hypertension and insulin resistance. In addition to the well-established link between increasing body weight and stone formation, studies have shown an independent correlation between the other key elements of metabolic syndrome and kidney stones. A large, prospective study of three cohorts (from the Health Professionals Follow-up Study, the Nurses' Health Study I and the Nurses' Health Study II) identified an increased risk of kidney stones in patients with type II diabetes mellitus (T2DM).[13] Cross-sectional analysis revealed that, in those with T2DM, the relative risk of stone formation was 1.6 in younger women, 1.38 in older women, and 1.31 in men, compared with the risks in those without T2DM.[13]

In light of these findings, it has been suggested that nephrolithiasis is a systemic disorder. Indeed, multiple studies have highlighted the link between metabolic syndrome and stones.[11–14] The mechanism of this association might be that decreased urinary pH resulting from insulin resistance leads to the development of uric acid stones.[12,15,16] One cross-sectional study of 148 patients characterized low urinary pH as a unique feature and presentation of an insulin-resistant state in patients with nephrolithiasis. In fact, 24 h urine pH was inversely correlated with level of insulin resistance.[16] In this setting, kidney stones do not necessarily develop because of hyperuricosuria, but rather occur as a result of insulin resistance, which leads to impaired renal excretion of ammonia and consequently results in acidic urine.[12] Acidic urine leads to elevated concentrations of insoluble uric acid, causing the precipitation of uric-acid-containing stones.[12,17]

Bariatric surgery patients

Obesity, a risk factor for urolithiasis, is successfully treated with bariatric surgery. Bariatric surgery procedures, however, further compound the risk of urolithiasis. The risk of stone formation following bariatric surgery is well documented: patients who have undergone bariatric surgery show a twofold increased risk of kidney stone formation compared with similarly obese patients who have not undergone bariatric surgery.[7–10] Lieske *et al.*[7] investigated whether bariatric surgery affects kidney stone risk by matching 762 obese individuals who underwent bariatric surgery with equally obese individuals who did not undergo surgery. Over a mean follow-up period of 6 years, new kidney stone formation was higher in patients who underwent bariatric surgery (11%) than in obese controls (4.3%). Lieske *et al.*[7] highlight a link between RYGB and stone formation, and reveal that more-malabsorptive procedures (such as very-long-limb RYGB or biliopancreatic

diversion with duodenal switch [Figure 3]) increase the risk of new stone formation further, even when controlling for obesity; the hazard ratio of stones in patients undergoing RYGB (standard surgery) was 2.15, while the hazard ratio of stones in those undergoing the more-malabsorptive-type procedures was 4.15.[7]

The risk of nephrolithiasis is reported as being highest in patients who have undergone more-malabsorptive operations, such as very-long-limb RYGB or biliopancreatic diversion with duodenal switch (Figure 3), next highest in patients who have undergone standard RYGB (Figure 1), and lowest in those who have had restrictive surgery, such as sleeve gastrectomy (Figure 2).[7,18] In fact, restrictive surgeries such as gastric banding might pose little to no threat of nephrolithiasis compared with bypass procedures.[18,19] Other large studies have also described the effects of bariatric surgery on the risk of stone formation. An assessment of 4,639 patients by Matlaga *et al.*[8] found that obese individuals with a history of gastric bypass surgery had a significantly increased risk of stone formation compared with obese controls (7.65% versus 4.63%).

Timeline of stone formation

Several long-term studies have elucidated the timing of nephrolithiasis occurrence following bariatric surgery. The literature reveals that the increased risk of stones ensues relatively rapidly after surgery and is sustained. Mean reported times to first stone episode range from 1.5 years to 2 years after surgery, and increased risk has been described up to 10 years following surgery.[7,8] Up to one in five patients undergoing bariatric surgery will have developed kidney stones after a follow-up period of 10 years after surgery.[7] Increases in urinary excretion of oxalate can occur as early as 3 months after the operation and urinary oxalate excretion remains high for several years following surgery; additionally, the prevalence of hypocitraturia increases dramatically over time after surgery.[20] Several studies have described the occurrence of *de novo* hyperoxaluria in approximately half of patients who have undergone RYGB operations, with these new metabolic derangements occurring in patients without any prior history of stones.[20,21]

Pathogenesis of stone formation

The events leading up to lithogenesis in patients who have undergone bariatric surgery are probably multifactorial. Pathogenic mechanisms include fat malabsorption, increased oxalate absorption, and, possibly, changes in the gut flora.[22,23] In patients who have undergone bariatric surgery, fat is malabsorbed, and calcium binds to fatty acids *in lieu* of oxalate, via saponification. The availability of calcium to bind oxalate is therefore reduced, which in turn increases the amount of unbound oxalate that can then be absorbed in the ileum.[6] In addition, some evidence exists to indicate that the exposure to unconjugated bile acids in patients with RYGB can lead to increased oxalate permeability in the colon, further compounding increases in oxalate absorption.[9] Increased absorption of oxalate leads to elevated urinary excretion of oxalate, a key event in the formation of calcium oxalate stones.

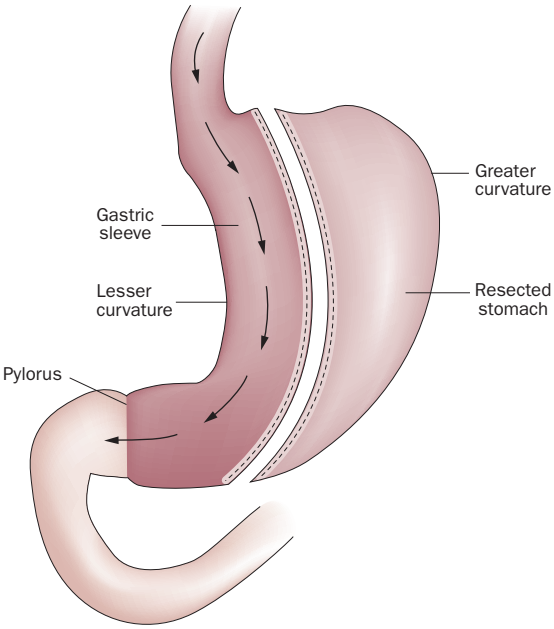

Figure 2 | Sleeve gastrectomy, the second most commonly performed restrictive bariatric surgery. This procedure is a restrictive procedure in which a tubular stomach is created following the removal of the greater curvature. The arrows show the passage of nutrients.

Risk of chronic kidney disease

The impact of kidney stones on renal function has yet to be clearly defined. Traditionally, chronic kidney disease (CKD) in the setting of stone disease was attributed to the deleterious effects of infection-induced staghorn kidney stones.[24,25] In a case–control study including 548 patients with end-stage renal disease (ESRD), 16.8% of patients had a history of nephrolithiasis compared with 6.4% of controls (odds ratio 1.9).[26] Kidney stones have been described as the cause of approximately 1% of cases of ESRD overall.[14,27] In light of the rise in use of bariatric surgery for obesity and the subsequent increased ongoing risk of stone formation, it is important to determine whether different bariatric operations are associated with different risks of CKD. The 2014 study by Lieske and co-workers[7] comparing 762 patients who had undergone bariatric surgery with equally obese controls showed that although both RYGB and malabsorptive procedures were associated with an increased risk of kidney stones, only malabsorptive bariatric procedures were associated with an increased risk of CKD (adjusted hazard ratio 1.96). Nelson *et al.*[6] also reported an increased risk of oxalate nephropathy in patients who have undergone bariatric surgery, with two patients ultimately advancing to ESRD. Although further studies are required to fully define the effect of RYGB on the risk of CKD and ESRD, it can be concluded that patients undergoing more-malabsorptive procedures require closer follow-up than those undergoing standard RYGB.

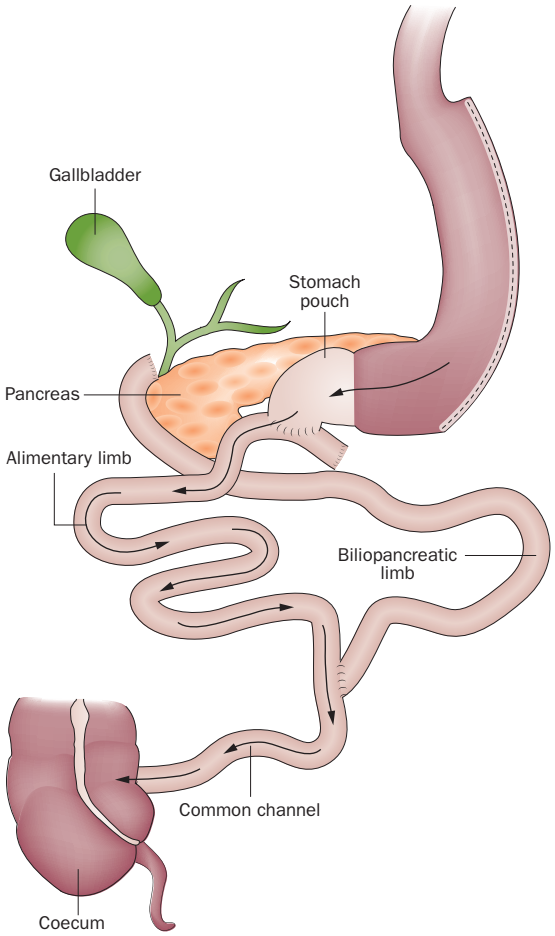

Figure 3 | Biliopancreatic diversion with duodenal switch, a procedure that is both restrictive and malabsorptive. A subtotal sleeve gastrectomy is performed first. The duodenum is then divided a short distance below the pyloric sphincter. The small intestine is divided more distally, forming an alimentary limb (carrying nutrients, shown by arrows) and a biliopancreatic limb (carrying pancreatic and biliary fluids). The alimentary limb is connected to the duodenum and the biliopancreatic limb is connected to the ileum. The two limbs join and nutrients are absorbed in the very short common channel; therefore, caloric absorption is limited.

24 h urine analysis

Obese individuals

Several large studies have investigated whether particular 24 h urine profiles predispose obese individuals to kidney stone formation but the results are somewhat variable. In a large US study of a national database that included 5,942 obese and nonobese individuals with urinary stone disease, Powell *et al.*[28] found that obese stone formers generally have a lithogenic profile with increased absolute excretion of all urinary metabolites, including calcium, oxalate, uric acid, sodium, magnesium, sulphate, phosphate and cystine compared with nonobese stone formers. However, the obese stone-forming patients also had increased urine volume compared with the non-obese stone formers; after correction for urine volume, only urinary concentrations of sodium, sulphate, phosphate, oxalate, and uric acid were found to be significantly different between obese and nonobese individuals. In addition, obese patients were found to have a lower urinary pH than did nonobese patients.[28] Negri *et al.*[29] studied 799 patients who developed kidney stones and found that increasing BMI was associated with an increase in urinary uric acid and oxalate, a decrease in urinary pH, but no change in urinary calcium.

Taylor *et al.*[11] made similar observations in their analysis of data from the Health Professionals Follow-up Study and the Nurses' Health Studies, and reported a trend for urinary calcium increasing with increasing BMI that disappeared after adjusting for urinary sodium and phosphorus. This finding led the idea that increased calcium in the urine in obese individuals might not be an intrinsic consequence of obesity, but rather the result of dietary choices.[11]

An association between decreased urinary pH, which promotes stone formation, and increased body weight has been shown in several large studies.[30,31] In particular, truncal fat seems to be associated with urinary pH.[32] The reason for this inverse relationship between urinary pH and BMI in patients with urolithiasis is not well defined. It has been hypothesized that the insulin resistance that occurs in obese individuals leads to decreased ammonium production in the proximal tubule, which in turn results in a decrease in urinary pH.[30] This effect may be gender specific as the inverse relationship between urinary pH and BMI has been reported in men only.[29,33]

Although some of the changes in urine profile that are associated with kidney stone formation in obese individuals are still unclear, in general it seems that a combination of increases in lithogenic factors such as increased urinary excretion of oxalate and uric acid and decreased urine pH with no significant increase in stone inhibitors (such as citrate) create a favourable milieu for stone formation.

Bariatric surgery patients

Several studies over the past decade have demonstrated changes occurring in urinary profiles following bariatric surgery that explain the increased risk of stone formation in this patient group. These changes have usually been increased urinary excretion of oxalate, decreased urine volume, decreased citrate excretion and decreased urine calcium excretion. In a retrospective study involving 132 patients, Asplin and Coe[34] compared the urine profiles of patients who had undergone modern bariatric surgery (banding or RYGB), jejunoileal bypass, patients with routine kidney stones and healthy individuals. Mean urine oxalate excretion was significantly higher in patients who had undergone modern bariatric surgery (83 mg per day) than in patients with routine kidney stones and in healthy individuals (39 mg per day and 34 mg per day, respectively). Patients who had undergone jejunoileal bypass, a procedure that has since been replaced by banding or RYGB owing to its high complication rate, had the highest levels of urinary oxalate excretion (103 mg per day).[34] Urine supersaturation of calcium oxalate was also higher in patients treated with bariatric surgery than in patients in the other groups.

Box 1 | Management of stones after bariatric surgery

Prevention of stones is paramount

Dietary considerations

- Counsel patients to limit dietary oxalate, sodium, and animal protein intake
- Consider calcium supplementation
- Encourage fluid intake; citrate-containing beverages are helpful in hypocitraturic patients

Medical therapy should be targeted at the underlying metabolic abnormality

- Potassium citrate, 60–120 mEq per day (liquid form, in three divided doses) should be given to those with recurrent stones and urinary findings of low pH, hypocitraturia and elevated supersaturation of calcium oxalate
- Allopurinol can be considered in patients who have uric acid stones and hyperuricemia or hyperuricosuria that do not respond to alkalinization
- Probiotic restoration of gut microflora has therapeutic potential

In a small cross-sectional study, Sinha *et al.*[35] analysed urinary profiles preoperatively, 6 months postoperatively, and at 12 months postoperatively in 20 patients who underwent RYGB surgery. Although changes were minimal at 6 months, by 12 months the researchers found significant decreases in urinary citrate and calcium levels and corresponding increases in urinary oxalate. In a long-term prospective study performed over 2 years ($n = 21$), Duffey *et al.*[20] followed patients before and after RYGB and made similar observations of increased urinary oxalate excretion and hypocitraturia following RYGB. Duffey *et al.*[20] found no significant difference in urinary supersaturation of calcium oxalate on 24 h urine collection after 1 year of follow-up in patients who had undergone bariatric surgery, although they had found that supersaturation increased early in the postoperative period (3 months after surgery). The difference between urinary supersaturation of calcium oxalate at 3 months and 1–2 years was attributed to an increase in urine volume over time, probably a result of an increased ability to increase fluid intake as the stomach pouch expands.[20] In a larger, prospective study involving 151 obese patients who underwent RYGB, Valezi *et al.*[36] further supported the consistent findings of the lithogenic urinary profile occurring after surgery—that is, increased urinary oxalate and uric acid, with decreased urinary pH, citrate, calcium, and magnesium.

Urinary profiles comparing restrictive bariatric procedures with RYGB consistently suggest that risk of stone formation might be lower when restrictive techniques are used. Semins *et al.*[37] compared the urinary profiles of 18 patients who underwent restrictive bariatric procedures (gastric banding and sleeve gastrectomy) with the urinary profiles of 54 patients who underwent RYGB. Patients who underwent restrictive bariatric procedures had significantly lower 24 h urinary oxalate excretion compared with patients who underwent RYGB (35 mg versus 61 mg) at the point of urine collection (at least 6 months after surgery).[37] Likewise, in a similar comparison of patients who had undergone RYGB and patients who had undergone gastric banding procedures, Penniston *et al.*[19] found that, although patients in both groups had similarly low urine volumes, urinary oxalate excretion was higher and urinary citrate excretion was lower in the patients who had undergone RYGB.

Overall, the clinical data shows that changes in urinary oxalate, urinary citrate, and urine volume contribute to the increased risk of nephrolithiasis in patients who have undergone bariatric surgery.

Management of stones after surgery

The management of stones after surgery involves both dietary considerations and medical therapy (Box 1).

Dietary recommendations

The risk of complications associated with surgical intervention is high in the bariatric surgery population (as it is in other obese populations), so there is a great need for preventive measures.[38] Dietary counselling can have an important role in the prevention of stones, and the roles of dietary calcium and dietary oxalate in particular should be considered. Although calcium supplementation has been historically linked with an increased risk of nephrolithiasis, current understanding is that calcium should not be restricted in patients who have undergone bariatric surgery. It is possible that calcium restriction leads to an increase in unbound oxalate in stone formers.[22] In a study of patients with recurrent calcium oxalate stones who had not undergone bariatric surgery, Borghi *et al.*[39] found that those who were randomized to a low-sodium, low-animal-protein and unrestricted-calcium diet reduced their stone episodes by 50% compared with those randomized to a restricted-calcium regimen. Evidence also exists to indicate that, although high dietary intake of calcium is associated with a reduced risk of kidney stones, taking calcium supplements might increase the risk of kidney stones.[40] However, the type of calcium supplementation preparation is relevant: although any calcium supplementation has the capacity to increase urinary calcium excretion, calcium citrate might be a safer option than calcium carbonate for patients at risk of developing calcium-containing stones. In fact, one study on non-stone-forming individuals found that although calcium citrate supplementation does lead to increased urinary calcium excretion at 1 month following initiation of supplementation, this effect is attenuated with long-term supplementation (3 months).[41] In addition, the resultant decrease in urinary phosphate with calcium citrate supplementation and the stone-inhibitory effects of citrate might protect against stone formation.[41] In a randomized, double-blind crossover study of 19 patients who had undergone RYGB, calcium citrate was found to have better bioavailability than did calcium carbonate.[42] This finding is probably related to the fact that the absorption of calcium carbonate is more dependent on gastric acid secretion than is absorption of calcium citrate, and that gastric acid secretion might be reduced in patients who have undergone RYGB.[42] Although these studies were small, calcium supplementation is especially relevant in patients who have undergone bariatric surgery, as there is an increased risk of bone loss and hypocitraturia is common.[22] Capsules are the preferred delivery method and patients should be advised to take calcium supplements with meals, as such timing means that a rise in urinary calcium oxalate supersaturation is avoided.[22]

The true effects of dietary oxalate on urinary oxalate levels are still uncertain. In healthy individuals, only 10–15% of urinary oxalate stems from food intake.[22] Dietary oxalate restriction can lead to a small alteration in the urinary excretion of oxalate, which might be especially helpful in patients who have undergone bariatric surgery and in patients with enteric hyperoxaluria. Indeed, evidence exists to indicate that patients with a history of bariatric surgery respond differently to a dietary oxalate load compared with patients who have not undergone such surgery. Froeder *et al.*[43] performed oxalate load testing on 22 morbidly obese patients and on 22 patients at a median of 2 years after bariatric surgery and found that the mean increase in oxaluria in response to a specific dietary oxalate load was significantly greater in bariatric surgery patients than in morbidly obese individuals. Patients with a history of bariatric surgery should be instructed to limit foods containing high levels of oxalate, including nuts, berries, chocolate, tea, and certain vegetables, including spinach, beets, rhubarb, and okra.[22,44] Providing patients with pamphlets containing lists of foods with both high and low oxalate contents might be helpful.

Sodium restriction has a role in reducing the risk of stone formation. Although dietary sodium limitation has not been evaluated specifically in patients who have undergone bariatric surgery, there is evidence that a high-sodium diet can increase urinary calcium excretion, decrease urinary citrate excretion and promote the precipitation of calcium salts in the urine.[22,45] Additionally, it is important that patients who have undergone bariatric surgery limit consumption of animal protein, as protein loading can exacerbate hyperoxaluria and hyperuricosuria in patients who form kidney stones.[46]

Patients undergoing bariatric surgery are also at risk of hypomagnesiuria, which might exacerbate risk of stone formation. As magnesium forms complexes with oxalate, low magnesium in the urine has the potential to increase the saturation of calcium oxalate, theoretically precipitating stone formation.[22,47] Although some evidence indicates that magnesium supplementation should be considered in patients who have undergone bariatric surgery and have hyperoxaluria and hypomagnesiuria, the data on magnesium supplementation are conflicting.[22] Ettinger *et al.*[48] found that magnesium supplementation did not reduce the risk of stones in recurrent calcium stone formers. Magnesium gluconate 0.5–1 g, taken three times a day, could be considered in some patients.[22] The possible beneficial effects of magnesium supplementation must be weighed up against the risk of increased hypercalciuria and the adverse effect of worsening diarrhoea.[22,48]

Fluid intake

Patients who have undergone bariatric surgery are also prone to low urine volume, which can be compounded by occupational and psychosocial factors that limit access to fluid intake.[43] Given the increased risk for volume depletion in these patients, they should be counselled on appropriate fluid intake with special attention to the need for high consumption of water and the avoidance of beverages containing high levels of oxalate, such as cola and other soft drinks that contain phosphoric acid.[22] Citrus-containing juices, including lemonade, can be considered in patients with hypocitraturia in order to increase urinary citrate excretion and can aid in increasing fluid intake volumes. Patients should be encouraged to drink enough liquids to maintain a urine output above 2.5 l per day.[22]

Medical therapy

Medical therapy is another option in the management of patients who have nephrolithiasis after bariatric surgery. Medical therapy with potassium citrate or allopurinol should be targeted at the underlying physiologic abnormality and specific urinary chemistries. Thiazide diuretics—although commonly used in the treatment of nephrolithiasis—are not very helpful in patients after bariatric surgery, as they are indicated for patients with hypercalciuria. Potassium citrate has an important role in correcting hypocitraturia and raising urinary pH, both of which are common derangements in patients who have undergone bariatric surgery.[22] Potassium citrate can also be beneficial in patients with elevated supersaturation of calcium oxalate.[22] In addition, patients with malabsorption might exhibit metabolic acidosis and hypokalaemia, which can also be managed with potassium citrate. Potassium citrate should be administered in three divided doses (60–120 mEq per day). Liquid forms are preferable to pill forms in post-bariatric-surgery patients, as they likely have better absorption compared with slow-release pills in those with fast gastrointestinal transit.[22] Although compliance may be limited by gastrointestinal upset in some patients, potassium citrate is relatively well tolerated and has a good adverse effect profile.[49] Compliance might be improved by using a sustained-release once-daily formulation (Urocit-K® 15 mEq, Mission Pharmacal Company, San Antonio, TX, USA). The beneficial effects of potassium citrate must be weighed against the potential risk of rare, but serious complications, such as hyperkalaemia, and cost should also be taken into account, as the medication is generally expensive. Allopurinol can be administered in patients who have uric acid stones and hyperuricaemia and have not responded appropriately to treatment with potassium citrate.[49] Allopurinol can also be considered in patients who have uric acid stones and hyperuricosuria and have not responded to alkalinization.[49] Adverse effects of allopurinol include rash and myalgia.[22]

Use of potassium citrate and other alkalinizing drugs has been studied in the management of kidney stones in patients who have undergone bariatric surgery. A two-phase, randomized cross-over study of 24 patients who had undergone RYGB compared the effect of a new combined formula of potassium citrate and calcium citrate, potassium–calcium citrate (PCC), with the effect of placebo on the crystallization of calcium and oxalate.[49] The study found that, compared with placebo, PCC increased urinary pH and citrate levels, thereby augmenting inhibitor activity against calcium–oxalate

agglomeration. The urinary saturation of uric acid was significantly reduced with PCC.[50] In addition, the calcium in PCC can replace malabsorptive losses, reducing parathyroid hormone activity and bone loss. Thus, PCC has the potential to target key metabolic derangements in patients who have undergone RYGB, and might be useful in patients with specific urinary chemistry findings, such as hypocitraturia; however, it is not commercially available. Cholestyramine 2–4 g per day with meals has been proposed as a therapeutic option for reducing the risk of stone formation in patients who have undergone bariatric surgery owing to its capacity to bind bile acids, which can limit gut exposure to bile acids and subsequent absorption of oxalate in the gut induced by bile salts.[22,44]

Studies performed in the 1980s investigated the role of pyridoxine (vitamin B6) supplementation in patients with hyperoxaluria. In one small study, eight out of 10 hyperoxaluric patients with kidney stones treated with pyridoxine 300 mg per day experienced a decrease in urinary oxalate.[51] Another small study of 12 patients with recurrent calcium oxalate stones found that pyridoxine at doses of 250–500 mg per day significantly reduced hyperoxaluria; eight of the 12 patients had no further stone episodes over 1.5 years of treatment.[52] However, these studies were not performed in patients with a history of bariatric surgery, and vitamin B6 is probably more helpful in the setting of primary hyperoxaluria type I, where it serves as a cofactor in a deficient enzymatic pathway.[44]

New treatment approaches

New directions for the management of kidney stones in patients who have undergone bariatric surgery include the targeting of the intestinal microenvironment.[53] Some authors have suggested that hyperoxaluria in patients who have undergone bariatric surgery and other patients with fat malabsorptive states might result from the loss of key intestinal microflora that would usually restrict absorption of oxalate by degrading it in the gut.[53] Alternatively, as a recent *in vitro* study indicated, *Oxalobacter formigenes* might interact with gut mucosa to promote the intestinal excretion of oxalate.[53,54] Thus, administering probiotic therapy might enable the intestinal microenvironment to be restored and might aid intestinal oxalate secretion. Animal models have shown some promise with use of *O. formigenes,* including improvement of urinary oxalate levels in just a few days.[55] However, it is still unclear whether *O. formigenes* can achieve colonization in the human intestine. In one study of 10 patients with enteric hyperoxaluria (including four patients with a history of RYGB), a mixture of lactic acid and bacteria administered in increasing doses led to a 19% decrease in urinary oxalate at 1 month and 24% decrease at 2 months. This effect was not sustained at the highest dose at 3 months, indicating that dosing needs to be optimized.[56] Further studies are necessary to establish the role of *O. formigenes* and other probiotic preparations in the treatment of enteric hyperoxaluria and the prevention of calcium oxalate stone formation.

Conclusions

Obesity is a worsening epidemic and rates of urolithiasis have increased in conjunction with rising obesity rates. Modern surgical procedures for weight loss, including RYGB and sleeve gastrectomy, are associated with an increased risk of kidney stone formation. The implications of stone disease on long-term renal function in patients who have undergone bariatric surgery requires further study, but patients with a history of malabsorptive procedures should be monitored carefully, as they are at highest risk of urolithiasis. Following bariatric surgery, fat is malabsorbed and binds calcium through saponification, leading to a decrease in the availability of calcium to bind oxalate. Elevated oxalate absorption, exacerbated by the disruption of gut mucosa by bile acid, leads to hyperoxaluria. Hypocitraturia and low urine volumes are also common in patients who have undergone bariatric surgery. These urinary aberrations can lead to kidney stone events within the first 2 years following bariatric surgery and may be sustained. Key aspects of management to prevent kidney stones in patients who have undergone bariatric surgery include dietary prevention through oxalate and sodium limitation. Patients who have undergone bariatric surgery might also require calcium supplementation owing to decreased calcium absorption. Fluid intake should be maintained above 2.5 l per day and citrate-containing juices might be a helpful supplementary therapy. Potassium citrate is useful in patients who have recurrent stones and urinary findings of low pH, hypocitraturia and elevated supersaturation of calcium oxalate. Allopurinol can be considered in patients who have uric acid stones and hyperuricemia or hyperuricosuria that do not respond to alkalinization with potassium citrate. Probiotic restoration of the gut microflora represents a promising new area of study in the management of kidney stones in the bariatric surgery population.

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Author contributions

S.T. and V.G. researched data for the article and wrote the article. S.T. and M.M. provided a substantial contribution to the discussion of content for the article and reviewed/edited the article before submission.