Management of Hypercalciuria and Oxalates in the Prevention of Stone Recurrence

88

John R. Asplin

Abstract

Urinary excretion of calcium and oxalate are two of the critical determinants of urine supersaturation of calcium oxalate salts and the risk of calcium oxalate stone formation. Therefore, treatment to reduce stone recurrence is focused on lowering the excretion of these lithogenic factors. Both diet and medication can lower urine calcium. Thiazide diuretics have been shown to reduce stone recurrence in randomized controlled trials and have the added benefit of improving bone mineral density. Citrate and bisphosphonates can lower urine calcium modestly but have not been well studied in hypercalciuric stone disease. Treatments to lower oxalate are not as well documented as are those for hypercalciuria. For idiopathic hyperoxaluria, pyridoxine and magnesium have been proposed as therapies, but there is conflicting data regarding their effectiveness. In enteric hyperoxaluria, low-oxalate diets and calcium supplements to bind dietary oxalate are the standard therapy. There is great interest in the use of oxalate-degrading bacteria as probiotics to treat hyperoxaluria, but human data is limited at this time.

Keywords

Hypercalciuria • Hyperoxaluria • Urolithiasis • Thiazide • Citrate • Bisphosphonate • Probiotic • Enteric hyperoxaluria • Supersaturation • Calcium • Oxalate

Introduction

Calcium is the most common component of human kidney stones. Approximately 85 % of calcium stones are predominantly calcium oxalate, either the monohydrate or dihydrate salt. Saturation is the physical chemical driving force for crystallization and can be expressed as the ratio of the ion activity products of the components of the salt of interest to its solubility [1]. A supersaturated solution is a requirement for crystals to form and grow. Urine concentrations of calcium and oxalate are the key determinants of saturation of calcium oxalate in the urine. Other urine components such as citrate, phosphate, and magnesium will affect saturation, but not to the level of either calcium or oxalate [2]. Prevailing urine saturation has been shown to correlate with the types of stones patients actually form [3]. Thus, our treatments to prevent stone formation are mainly focused on lowering saturation. Certainly, the standard recommendation to increase fluid intake to dilute urine will lower the concentration of all lithogenic components of the urine, lowering saturation and reducing stone risk. Reducing renal excretion of calcium and oxalate are the other primary goals in the treatment of calcium oxalate stones, both of which will reduce saturation. This chapter will address medical therapy to treat hypercalciuria and hyperoxaluria. Dietary therapy, which is of great importance in stone disease, has been covered in Chap. 86.

J.R. Asplin, M.D., FASN
Department of Medicine, University of Chicago,
Litholink Corporation, 2250 W Campbell Park Dr.,
Chicago, IL 60612, USA

Department of Medicine, University of Chicago,
Chicago, IL, USA
e-mail: asplinj@labcorp.com

J.J. Talati et al. (eds.), *Urolithiasis*,
DOI 10.1007/978-1-4471-4387-1_88, © Springer-Verlag London 2012

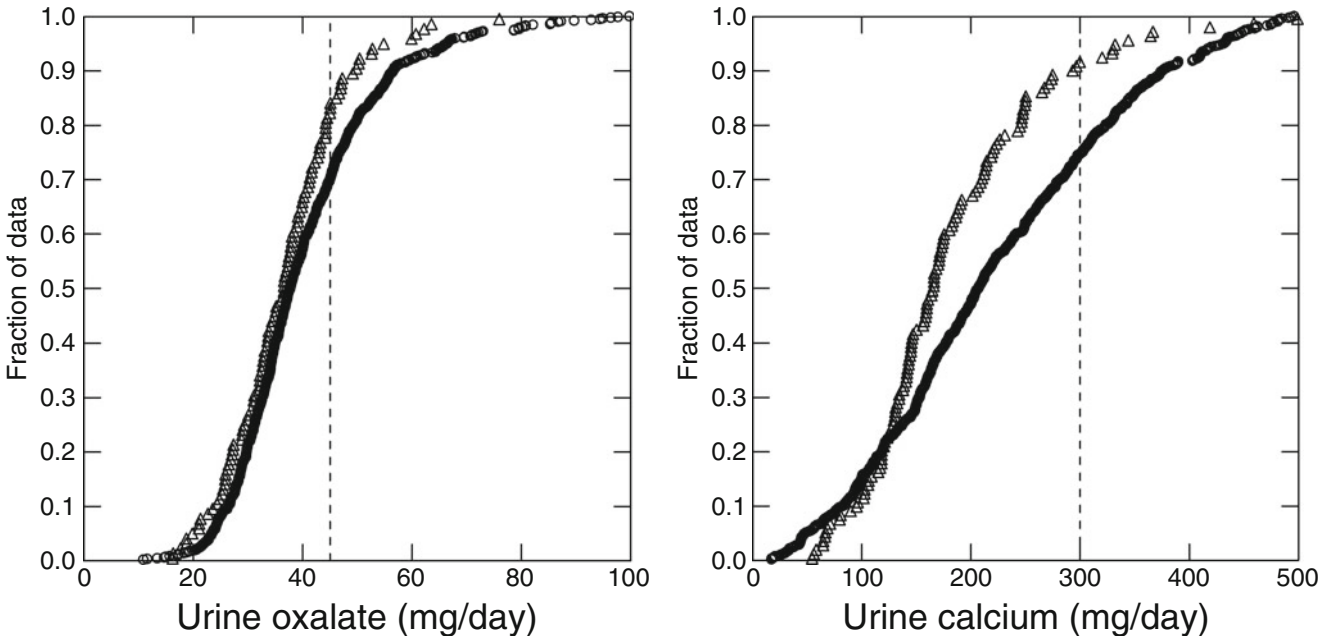

Fig. 88.1 Quantile plots of urine oxalate and urine calcium in men. Stone-forming patients (*circles*) have excretion rates shifted to the right of normal subjects (*triangles*). The right shift of patients is much greater for calcium excretion than that of oxalate excretion, where the distributions greatly overlap. The *vertical dashed line* identifies 45 mg/day for oxalate and 300 mg/day for calcium

Definition of Hypercalciuria and Hyperoxaluria

Most commonly, hypercalciuria is defined as an excretion of 300 mg/day in men or 250 mg/day in women, or as a ratio of the daily excretion to the patient's weight using 4 mg/kg as the upper limit. Other researchers use a definition of 200 mg/day when the patient is studied while consuming a low calcium, low sodium diet [4]. However, strict control of diet is required for this definition and is hard to achieve in routine clinical practice. For oxalate, a common definition of hyperoxaluria is greater than 45 mg/day (0.5 mmol/day), though some authors use a slightly lower value of 40 mg/day [5]. Overall, these definitions are useful in research in defining populations to be studied to understand pathophysiology and therapeutic interventions. In clinical practice, we need to recognize that reference ranges likely differ from one culture/country to another. Laboratory methods vary, particularly for oxalate, such that each lab should have ranges specific for the population and analytic method employed [6].

An important factor to recognize in the treatment of patients is that urine calcium and oxalate are not dichotomous variables and there is not a distinct level beyond which stone risk rises dramatically. Though hypercalciuria is the most common metabolic abnormality found in calcium stone formers, there is considerable overlap in urine calcium excretion in normal and stone-forming populations. For urine oxalate, there is only a mild difference between stone formers and normal subjects. As can be seen in Fig. 88.1, using data obtained from a commercial laboratory, the distribution of urine calcium is clearly shifted higher than non-stone-forming controls, though overlap is considerable. For oxalate, the shift is much less dramatic and overlap of the distributions is almost complete. Such data can lead to the conclusion that oxalate is not an important component of stone risk, but it needs to be recognized that stone risk is a continuous variable and increases as urine calcium and urine oxalate increase. Curhan et al. have reported that stone risk starts to increase well within the classically defined normal ranges for both oxalate and calcium [7]. It may be necessary to treat urine chemistries that are within the normal range, as lowering excretion to below the population mean may be required to lower saturation sufficiently to prevent stone formation. Historically, there has been more focus in treating urine calcium as both diet and medications were shown to lower urine calcium consistently. For hyperoxaluria, treatment effects have not been so clear but that does not mean lowering urine oxalate excretion would not be effective therapy for stone disease.

Throughout this chapter, the terms hypercalciuria and hyperoxaluria will be used but with recognition that stone risk increases as excretion of calcium and oxalate increases. Physicians may treat to lower urine calcium and/or oxalate even when they are within the "normal range."

Management of Hypercalciuria

Once hypercalciuria has been identified, the physician must determine the etiology. Idiopathic hypercalciuria is the most common cause of hypercalciuria in kidney stone patients. It is defined as excess urine calcium with normal serum

Table 88.1 Randomized prospective trials of thiazide and thiazide-like diuretics in calcium urolithiasis

Study	Drug[a]	*N*	Duration (years)	Control (%)	Drug (%)	*P* value
Scholz et al. [10]	HCTZ 25 mg bid	51	1	23	24	NS
Brocks et al. [9]	BFMT 2.5 mg tid	62	1.5	17	15	NS
Ohkawa et al. [12]	TCM 4 mg qd	175	2	14	8	$0.05<p<0.1$
Mortensen et al. [11]	BFMT 2.5 mg tid	22	2	40	0	$0.05<p<0.1$
Ettinger et al. [13]	CTD 25 or 50 mg qd	73	3	50	20	$p<0.05$
Laerum and Larsen [14]	HCTZ 25 mg bid	50	3	55	25	$p<0.05$
Borghi et al. [15]	IND 2.5 mg qd	50	3	43	16	$p<0.02$

Results of each study are expressed as the percent of subjects who had at least one stone during follow-up for the nonthiazide group (control) compared to the active treatment group (drug)
[a]*HCTZ* hydrochlorothiazide, *BFMT* bendroflumethiazide, *TCM* trichlormethiazide, *CTD* chlorthalidone, *IND* indapamide.

calcium, in the absence of systemic disorders known to affect calcium metabolism. If systemic disorders that lead to excess urine calcium excretion are present, such as primary hyperparathyroidism or sarcoid, then the treatment should be directed at the primary disorder, if possible.

The standard pharmaceutical treatment of hypercalciuria is the use of thiazide diuretics. Thiazide diuretics lower urine calcium excretion, mainly by inducing a state of volume depletion, which results in increased proximal tubule reabsorption of calcium [8]. There may also be a direct effect on tubule reabsorption in the distal convoluted tubule. Based on the hypocalciuric effect of thiazides, a number of prospective randomized trials of thiazide with reduction of stone formation as the primary endpoint have been performed. It has been said that the results of the thiazide trials are conflicting and that it is not clear if thiazides reduce stone recurrence. However, as can be seen in Table 88.1, though there are multiple studies of thiazide, there are only three trials that have lasted 3 years. This is a critical point, as studies with a stone formation outcome require sufficient time from entry to accumulate adequate stone events to detect a treatment effect. The two trials that were less than 2 years were negative [9, 10]; the trials of 2 years duration had a borderline statistical significance for the positive effect found for thiazides [11, 12]. The three 3-year prospective randomized trials all showed a significant reduction in stone events in the thiazide group [13–15]. Of note, the trials by Ettinger et al. and Laerum and Larsen used calcium stone formation, not hypercalciuria, as entry criteria. That they were able to show a reduction in stone events suggests that patients do not have to meet the standard criteria of hypercalciuria to receive benefits of treatment that lower urine calcium.

In the thiazide trials, note that two of the thiazides used were chlorthalidone and indapamide, both of which have very long half-lives, providing continuous action throughout the day. The positive study, which used a short-acting thiazide, was that of Laerum, who used hydrochlorothiazide but dosed the drug twice a day. In general, a long-acting drug like chlorthalidone or indapamide should be preferred, but if a short-acting thiazide is to be used, it should be used on a twice-a-day schedule. When using a thiazide, patients should be instructed to limit their sodium intake to 2,300–3,000 mg/day. Not only will salt restriction itself lower urine calcium excretion but it will enhance the action of the diuretic. If patients eat large amounts of salt while taking thiazide, they will prevent the volume depletion the drug needs to induce in order to work. Plus, the large salt load in combination with the diuretic will greatly enhance renal potassium wasting. Patients on thiazide should have blood potassium levels measured to monitor for hypokalemia. Hypokalemia can reduce urine citrate levels, blunting any benefit obtained from lowering urine calcium [16]. Not all the thiazide trials made an attempt to maintain serum potassium in the normal range. Attention to such detail in clinical practice may allow the physician to obtain even better results than the randomized trials. Repletion of potassium losses can be accomplished with oral potassium salts, with a goal of keeping serum potassium above 4.0 mmol/l. An alternative is to use a potassium sparing diuretic. Amiloride is the preferred potassium sparing diuretic since triamterene has been shown to crystallize in the urinary tract and can be a component of stones itself [17].

In addition to reducing stone formation, thiazides provide the added benefit of improving bone mineral density. Thiazides not only reduce urine calcium but also increase net calcium balance [18]. Patients with low bone mineral density from hypercalciuria have been shown to increase bone mineral density during treatment with thiazides [19]. Though there are no direct fracture outcomes for hypercalciuric patients treated with thiazide, large cohort studies of patients with hypertension who were treated with thiazide diuretics have been shown to have lower fracture rates than matched controls who did not receive thiazide [20, 21]. The well-documented reduction in stones and the overall benefit to bone health make thiazide diuretics the primary treatment for hypercalciuric patients with nephrolithiasis.

Though low sodium, low-protein diets, and thiazide diuretics are clearly the primary therapies for hypercalciuria,

Table 88.2 Effect of alendronate on urine calcium and bone mineral density in patients with hypercalciuria

Study	Subjects[a]	Duration	UCa baseline[b]	UCa on therapy	Spine BMD baseline (g/cm^2)	Spine BMD on therapy (g/cm^2)
Weisinger et al. [29]	18 HCSF	1 year	277 ± 28 mg/g	202 ± 26 mg/g*	1.16 ± 0.23	1.20 ± 0.25*
Heller et al. [28]	9 HCSF	17 days	140 ± 70 mg/g	60 ± 40 mg/g*	NA	NA
Giusti et al. [30]	25 HCPM	1 year	379 ± 79 mg/day	279 ± 68 mg/day*	0.76 ± 0.09	0.80 ± 0.08*

Urine calcium fell significantly with alendronate treatment in all studies. The bone mineral density increased significantly in both 1 year studies
[a]*HCSF* hypercalciuric stone formers, *HCPM* hypercalciuric postmenopausal women
[b]mg/g, mg of urine calcium per gram of creatinine
*$p < 0.05$

there are other drugs that may have beneficial effects in hypercalciuria. Alkali, usually provided in the form of potassium citrate salts, has a modest effect on urine calcium excretion. Since diets rich in animal protein result in a dietary acid load that increases renal calcium excretion, providing alkali to neutralize metabolic acid production can lower urine calcium excretion. In well-controlled studies where diet was fixed, potassium citrate in doses of 60–80 meq/day reduced calcium excretion by 20–25 % [22, 23]. In the prospective trials of citrate therapy, no significant fall in urine calcium was noted during the 3 years of follow-up, suggesting the magnitude of the alkali effect is modest and difficult to detect when diet is not fixed [24, 25]. Potassium citrate is not indicated as the primary treatment for hypercalciuria but may provide additional benefit in lowering urine calcium when used to maintain potassium stores in patients treated with thiazide [26]. The one caveat concerning use of alkali in hypercalciuric patients is that increasing urine pH above 6.3 can promote calcium phosphate stone formation. If alkali is used, the clinician needs to ensure that urine calcium excretion is being lowered sufficiently by therapy in order to offset the negative effects of a high urine pH.

Bisphosphonates reduce bone resorption and are the most common drugs used to treat osteoporosis. Since reduced bone mineral density and increased lability of bone mineral are frequent findings in hypercalciuric stone formers, it is reasonable to consider therapy directed at the bone component to hypercalciuria [27, 28]. There are a small number of papers that have reported the effects of bisphosphonates in hypercalciuric stone patients. The papers summarized in Table 88.2 do not include studies done with earlier forms of bisphosphonates such as etidronate, which is seldom used today. The studies have shown a modest improvement in urine calcium on bisphosphonates, and two of them have shown an improvement in bone mineral density after a year of treatment [28–30]. There are no studies where a reduction in kidney stone formation was used as an end point, and none of these studies included a control group. More research is necessary before the role of bisphosphonates in hypercalciuric stone disease is clearly established. At the present time, the use of these drugs should be restricted to hypercalciuric stone patients who have low bone mineral density that has not responded adequately to normal calcium diet and a thiazide diuretic.

Management of Hyperoxaluria

In most patients, urine oxalate is only modestly elevated and is likely dietary in origin. However, more severe forms of hyperoxaluria do exist and need to be identified as they can cause kidney damage and require more aggressive management. Enteric hyperoxaluria is seen with intestinal disease in which fat malabsorption leads to increased oxalate absorption in the colon. Enteric hyperoxaluria may be seen in Crohn's disease or with extensive small bowel resection. In recent years, it has been recognized that a significant number of patients who have had bariatric surgery, either Roux-en-y gastric bypass or biliopancreatic diversion, will develop enteric hyperoxaluria [31, 32]. Primary hyperoxaluria is an autosomal recessive disorder characterized by severe hyperoxaluria, kidney stones, and potentially loss of kidney function. To date, three types of primary hyperoxaluria have been identified [33]. When urine oxalate is greater than 80 mg/day in an adult without bowel disease, primary hyperoxaluria needs to be considered in the differential diagnosis. In children, significant hyperoxaluria (adjusted for body size or creatinine excretion) demands evaluation for primary hyperoxaluria. In reviewing treatment options for hyperoxaluria, idiopathic hyperoxaluria will be considered first, and then specific comments will be made concerning enteric and primary hyperoxaluria.

Pyridoxine has been recommended as a treatment of hyperoxaluria, because pyridoxine is a cofactor for the enzyme alanine-glyoxylate aminotransferase (AGT), which converts glyoxylate to glycine, reducing formation of oxalate. There are a number of trials of pyridoxine in stone disease, but none have prospectively shown a reduction in stone formation using an adequate control group. A few studies showed reduction in urine oxalate with pyridoxine, but this was not a universal finding [34–37]. In some studies pyridoxine therapy was combined with magnesium supplements, making it impossible to isolate the pyridoxine effect. Two large prospective studies found a relationship of low

pyridoxine intake with incident stone formation in women, but not in men [38, 39]. More definitive studies are needed to define the role of pyridoxine in routine calcium oxalate stone disease. At modest doses of 5–25 mg/day, pyridoxine is well tolerated and can be used in patients who have hyperoxaluria unresponsive to dietary therapy, with recognition that there is not clear evidence favoring benefit.

Magnesium has been used as a treatment for urolithiasis because it may lower urine oxalate by complexing oxalate in the intestine [40], as well as acting as a calcium crystal inhibitor in the urine [41]. There are uncontrolled trials that report a benefit of magnesium therapy in reducing stone rates [42, 43], but there has been only one controlled trial of magnesium supplements in calcium stone disease, and it did not show a reduction in stone formation [13]. Unanswered is whether patients with hypomagnesuria [44] represent a subset of patients who may respond to magnesium supplements, since no trials have considered magnesium excretion as an entry criteria. Use of magnesium supplements is limited by diarrhea when magnesium dose exceeds 350–400 mg/day.

Oxalobacter formigenes is an anaerobic bacteria that is part of the normal intestinal flora and uses oxalate as its sole carbon source [45]. The potential of oxalate-degrading bacteria as a therapy for hyperoxaluria and calcium oxalate stones has been an area of active investigation. In a rat model of hyperoxaluria, Sidhu et al. showed *O. formigenes* delivered by gavage lowered urine oxalate excretion [46]. In a study using a rat model, Hatch et al. showed that the bacteria not only increase intestinal oxalate secretion by lowering luminal oxalate concentration but that bacterial homogenates can stimulate intestinal secretion of oxalate by upregulating transporters [47]. The secretory action of *O. formigenes* was confirmed in a mouse model of primary hyperoxaluria. No studies have been performed in humans to show if *O. formigenes* can stimulate intestinal oxalate secretion.

Lactic acid bacteria also have the capacity to degrade oxalate, though not as efficiently as *O. formigenes*. An uncontrolled trial of a probiotic preparation of lactic acid bacteria in six patients showed a significant reduction of urine oxalate [48]. In addition, a trial of escalating dose of the lactic acid preparation showed a modest reduction in urine oxalate excretion in patients with enteric hyperoxaluria [49]. However, a randomized control trial of the same probiotic did not show a lowering of urine oxalate in patients with hyperoxaluria and calcium oxalate stones [50]. Whether *O. formigenes* or lactic acid bacteria are truly effective therapies in hyperoxaluric stone, patients remain to be seen.

In patients with enteric hyperoxaluria, the control of oxalate is of utmost importance as loss of renal function is a risk. The pathophysiology of enteric hyperoxaluria depends on two alterations of intestinal function: (1) fat malabsorption leading to excess free fatty acids in the intestinal lumen which bind diet calcium, leading to more free oxalate available to be absorbed and (2) increased delivery of bile acids to the colon, leading to increased oxalate permeability of the colonic mucosa. Since excess urine oxalate is derived from the diet, intestinal oxalate absorption needs to be minimized. A low-oxalate diet limits oxalate available for absorption and low dietary fat will reduce free fatty acids to bind calcium. Increasing calcium intake increases intestinal calcium concentration, reducing oxalate bioavailability. Calcium supplements are usually required and need to be taken with meals to maximize binding to diet oxalate. Calcium citrate is preferred over calcium carbonate because patients who have altered stomach anatomy from bariatric surgery may not acidify stomach contents adequately to dissolve calcium carbonate pills. Though there is the concern that calcium excretion will increase, calcium absorption is often compromised in patients with small bowel disease, and the extra calcium provided will be essential to maintain skeletal integrity. Cholestyramine, which binds fatty acids and oxalate, has been shown to be useful in patients with hyperoxaluria from Crohn's disease but has not been studied in those with enteric hyperoxaluria from bariatric surgery.

Primary hyperoxaluria requires aggressive lifelong treatment in order to control recurrent stone formation and prevent progressive loss of kidney function. At one time, primary hyperoxaluria was felt to universally end in kidney failure, but data collected over the last two decades show that a large number of patients maintain adequate kidney function when treated early. Approximately, 25–30 % of patients with type 1 primary hyperoxaluria will respond to pyridoxine therapy with a significant reduction in urine oxalate excretion. In most patients with primary hyperoxaluria, we do not have a therapy to lower urine oxalate, so all effort is directed at minimizing the risk of calcium oxalate crystallization. Fluid intake is maximized and potassium citrate and neutral phosphate salts are prescribed [51, 52]. If kidney damage does develop, the patient should be considered for a liver transplant to correct the underlying metabolic defect. If kidney damage is severe, a kidney transplant may be done simultaneously.

Conclusion

Treatment of calcium oxalate stones is focused on lowering urine concentrations of calcium and oxalate, which can be accomplished by increasing fluid intake to create diluted urine or by lowering excretion rates of calcium and oxalate. Clinicians need to recognize that urine calcium and oxalate are continuous variables in regards to stone risk and patients often require treatment to lower excretion rates even though they do not meet a research definition of hypercalciuria or hyperoxaluria. Pharmacologic treatment is often needed in addition to diet to prevent stone recurrence. Thiazide diuretics lower urine calcium excretion and improve calcium balance.

There are three 3-year prospective randomized trials showing thiazide diuretics reduce calcium stone formation. Patients with urolithiasis and hypercalciuria are at increased risk of fracture; thiazides can improve bone mineral density in these patients. Citrate can lower urine calcium excretion by buffering metabolic acid production. The effect is modest so citrate is usually used as an adjunct to thiazide in the setting of hypercalciuria. Bisphosphonates reduce bone resorption and can lower urine calcium modestly. They have not been extensively studied in patients with urolithiasis so the role of bisphosphonates in treatment of urolithiasis is not well established. Medical therapy to lower urine oxalate is not well defined. Idiopathic hyperoxaluria has been treated with magnesium and/or pyridoxine supplementation. However, there are no prospective randomized trials to show that these therapies lower stone recurrence. Oxalate-degrading bacteria, used as probiotics, are an area of great interest. Though shown to be effective in animal models of hyperoxaluria, human trials are inconclusive at this time.

References

1. Werness PG, Brown CM, Smith LH, Finlayson B. EQUIL 2: a basic computer program for the calculation of urinary saturation. J Urol. 1985;134:1242–4.
2. Tiselius HG. An improved method for the routine biochemical evaluation of patients with recurrent calcium oxalate stone disease. Clin Chim Acta. 1982;122(3):409–18.
3. Asplin J, Parks J, Lingeman J, Kahnoski R, Mardis H, Lacey S, et al. Supersaturation and stone composition in a network of dispersed treatment sites. J Urol. 1998;159(6):1821–5.
4. Pak CY, Sakhaee K, Moe OW, Poindexter J, Adams-Huet B. Defining hypercalciuria in nephrolithiasis. Kidney Int. 2011;80(7):777–82.
5. Asplin JR. Hyperoxaluric calcium nephrolithiasis. Endocrinol Metab Clin North Am. 2002;31(4):927–49.
6. Maalouf NM, Adams HB, Pasch A, Lieske JC, Asplin JR, Siener R, et al. Variability in urinary oxalate measurements between six international laboratories. Nephrol Dial Transplant. 2011;26(12):3954–9.
7. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Twenty-four-hour urine chemistries and the risk of kidney stones among women and men. Kidney Int. 2001;59(6):2290–8.
8. Nijenhuis T, Vallon V, van der Kemp AW, Loffing J, Hoenderop JG, Bindels RJ. Enhanced passive Ca^{2+} reabsorption and reduced Mg^{2+} channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651–8.
9. Brocks P, Dahl C, Wolf H, Transbol I. Do thiazides prevent recurrent idiopathic renal calcium stones? Lancet. 1981;2(8238):124–5.
10. Scholz D, Schwille PO, Sigel A. Double-blind study with thiazide in recurrent calcium lithiasis. J Urol. 1982;128(5):903–7.
11. Mortensen JT, Schultz A, Ostergaard AH. Thiazides in the prophylactic treatment of recurrent idiopathic kidney stones. Int Urol Nephrol. 1986;18(3):265–9.
12. Ohkawa M, Tokunaga S, Nakashima T, Orito M, Hisazumi H. Thiazide treatment for calcium urolithiasis in patients with idiopathic hypercalciuria. Br J Urol. 1992;69(6):571–6.
13. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculous recurrence but magnesium hydroxide does not. J Urol. 1988;139:679–84.
14. Laerum E, Larsen S. Thiazide prophylaxis of urolithiasis: a double-blind study in general practice. Acta Med Scand. 1984;215:383–9.
15. Borghi L, Meschi T, Guerra A, Novarini A. Randomized prospective study of a nonthiazide diuretic, indapamide, in preventing calcium stone recurrences. J Cardiovasc Pharmacol. 1993;22 Suppl 6:S78–86.
16. Hamm LL. Renal handling of citrate. Kidney Int. 1990;38(4):728–35.
17. Ettinger B, Oldroyd NO, Sorgel F. Triamterene nephrolithiasis. JAMA. 1980;244(21):2443–5.
18. Coe FL, Parks JH, Bushinsky DA, Langman CB, Favus MJ. Chlorthalidone promotes mineral retention in patients with idiopathic hypercalciuria. Kidney Int. 1988;33(6):1140–6.
19. Adams J, Song C, Kantorovich V. Rapid recovery of bone mass in hypercalcuric, osteoporotic men treated with hydrochlorothiazide. Ann Intern Med. 1999;130:658–60.
20. Schoofs MW, van der Klift M, Hofman A, De Laet CE, Herings RM, Stijnen T, et al. Thiazide diuretics and the risk for hip fracture. Ann Intern Med. 2003;139(6):476–82.
21. LaCroix AZ, Wienpahl J, White LR, Wallace RB, Scherr PA, George LK, et al. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med. 1990;322(5):286–90.
22. Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. Kidney Int. 1983;24:348–52.
23. Sakhaee K, Alpern R, Jacobson HR, Pak CY. Contrasting effects of various potassium salts on renal citrate excretion. J Clin Endocrinol Metab. 1991;72(2):396–400.
24. Ettinger B, Pak CYC, Citron JT, Thomas C, Adams-Huet B, Vangessel A. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. J Urol. 1997;158:2069–73.
25. Barcelo P, Wuhl O, Servitge E, Roussaud A, Pak C. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. J Urol. 1993;150:1761–4.
26. Frassetto LA, Nash E, Morris Jr RC, Sebastian A. Comparative effects of potassium chloride and bicarbonate on thiazide-induced reduction in urinary calcium excretion. Kidney Int. 2000;58(2):748–52.
27. Pietschmann F, Breslau NA, Pak CY. Reduced vertebral bone density in hypercalciuric nephrolithiasis. J Bone Miner Res. 1992;7(12):1383–8.
28. Heller HJ, Zerwekh JE, Gottschalk FA, Pak CY. Reduced bone formation and relatively increased bone resorption in absorptive hypercalciuria. Kidney Int. 2007;71(8):808–15.
29. Weisinger JR, Alonzo E, Machado C, Carlini R, Martinis R, Paz-Martinez V, et al. Role of bones in the physiopathology of idiopathic hypercalciuria: effect of amino-bisphosphonate alendronate. Medicina (B Aires). 1997;57 Suppl 1:45–8.
30. Giusti A, Barone A, Pioli G, Girasole G, Siccardi V, Palummeri E, et al. Alendronate and indapamide alone or in combination in the management of hypercalciuria associated with osteoporosis: a randomized controlled trial of two drugs and three treatments. Nephrol Dial Transplant. 2009;24(5):1472–7.
31. Asplin JR, Coe FL. Hyperoxaluria in kidney stone formers treated with modern bariatric surgery. J Urol. 2007;177(2):565–9.
32. Patel BN, Passman CM, Fernandez A, Asplin JR, Coe FL, Kim SC, et al. Prevalence of hyperoxaluria after bariatric surgery. J Urol. 2009;181(1):161–6.
33. Belostotsky R, Seboun E, Idelson GH, Milliner DS, Becker-Cohen R, Rinat C, et al. Mutations in DHDPSL are responsible for primary hyperoxaluria type III. Am J Hum Genet. 2010;87(3):392–9.

34. Rattan V, Sidhu H, Vaidyanathan S, Thind SK, Nath R. Effect of combined supplementation of magnesium oxide and pyridoxine in calcium-oxalate stone formers. Urol Res. 1994;22(3):161–5.
35. Prien Sr EL, Gershoff SF. Magnesium oxide-pyridoxine therapy for recurrent calcium oxalate calculi. J Urol. 1974;112(4):509–12.
36. Edwards P, Nemat S, Rose GA. Effects of oral pyridoxine upon plasma and 24-hour urinary oxalate levels in normal subjects and stone formers with idiopathic hypercalciuria. Urol Res. 1990; 18(6):393–6.
37. Mitwalli A, Ayiomamitis A, Grass L, Oreopoulos DG. Control of hyperoxaluria with large doses of pyridoxine in patients with kidney stones. Int Urol Nephrol. 1988;20(4):353–9.
38. Curhan GC, Willett WC, Speizer FE, Stampfer MJ. Intake of vitamins B_6 and C and the risk of kidney stones in women. J Am Soc Nephrol. 1999;10(4):840–5.
39. Curhan GC, Willett WC, Rimm EB, Stampfer MJ. A prospective study of the intake of vitamins C and B_6, and the risk of kidney stones in men. J Urol. 1996;155(6):1847–51.
40. Berg W, Bothor C, Pirlich W, Janitzky V. Influence of magnesium on the absorption and excretion of calcium and oxalate ions. Eur Urol. 1986;12(4):274–82.
41. Bisaz S, Felix R, Neuman WF, Fleisch H. Quantitative determination of inhibitors of calcium phosphate precipitation in whole urine. Miner Electrolyte Metab. 1978;1:74–83.
42. Johansson G, Backman U, Danielson BG, Fellstrom B, Ljunghall S, Wikstrom B. Biochemical and clinical effects of the prophylactic treatment of renal calcium stones with magnesium hydroxide. J Urol. 1980;124(6):770–4.
43. Melnick I, Landes RR, Hoffman AA, Burch JF. Magnesium therapy for recurring calcium oxalate urinary calculi. J Urol. 1971;105: 119–22.
44. Preminger GM, Baker S, Peterson R, Poindexter J, Pak CYC. Hypomagnesiuric hypocitraturia: an apparent new entity for calcium nephrolithiasis. J Lithotr Stone Dis. 1989;1: 22–5.
45. Allison MJ, Dawson KA, Mayberry WR, Foss JG. *Oxalobacter formigenes* gen. nov., sp. nov.: oxalate-degrading anaerobes that inhabit the gastrointestinal tract. Arch Microbiol. 1985;141(1): 1–7.
46. Sidhu H, Allison MJ, Chow JM, Clark A, Peck AB. Rapid reversal of hyperoxaluria in a rat model after probiotic administration of *Oxalobacter formigenes*. J Urol. 2001;166(4):1487–91.
47. Hatch M, Cornelius J, Allison M, Sidhu H, Peck A, Freel RW. *Oxalobacter* sp. reduces urinary oxalate excretion by promoting enteric oxalate secretion. Kidney Int. 2006;69(4):691–8.
48. Campieri C, Campieri M, Bertuzzi V, Swennen E, Matteuzzi D, Stefoni S, et al. Reduction of oxaluria after an oral course of lactic acid bacteria at high concentration. Kidney Int. 2001;60(3): 1097–105.
49. Lieske JC, Goldfarb DS, De Simone C, Regnier C. Use of a probiotic to decrease enteric hyperoxaluria. Kidney Int. 2005;68(3): 1244–9.
50. Goldfarb DS, Modersizki F, Asplin JR. A randomized, controlled trial of lactic acid bacteria for idiopathic hypercalciuria. Clin J Am Soc Nephrol. 2007;2:745–9.
51. Leumann E, Hoppe B, Neuhaus T. Management of primary hyperoxaluria: efficacy of oral citrate administration. Pediatr Nephrol. 1993;7(2):207–11.
52. Milliner DS, Eickholt JT, Bergstralh EJ, Wilson DM, Smith LH. Results of long-term treatment with orthophosphate and pyridoxine in patients with primary hyperoxaluria. N Engl J Med. 1994;331(23): 1553–8.