Chemical pathology clinical investigation and management of nephrolithiasis

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Renal stones have afflicted humans for millennia but there is still no solution to this problem. This review discusses the laboratory and metabolic aspects of the clinical management of patients with renal stones, both primary and secondary in origin. First, non-pharmacological interventions such as increased fluid intake, decreased protein consumption, dietary changes in sodium, calcium, oxalate, potassium, purine, vitamins, and essential fatty acids are considered. Then specific pharmacological treatment to modify urine calcium, oxalate, urate, citrate, and acidity are considered. Finally, more unusual types of stone are examined.

Renal stones have afflicted humans for millennia. Early descriptions were present in the *Aphorisms of Hipparchus*. They are also extremely common: the lifetime risk for a white man is 12–15%, and for white women it is 5–6%,^{1,2} with lifetime recurrence rates of up to 50%.¹ The interval between recurrences is variable, with approximately 10% within one year, 35% in five years, and 50% by 10 years.² There are also significant ethnic variations in incidence, with urbanised black South Africans having a reported incidence of < 1%.^{3,4} However, nephrolithiasis is not a single disease: approximately 75% of stones are primarily calcium oxalate, but up to 50% of these include calcium hydroxyl phosphate (brushite or calcium hydroxyapatite), in trace or greater amounts;⁵ 10–20% of stones are composed of magnesium ammonium phosphate (struvite or triple phosphate); 5% are composed of urate; and 1–2% are composed of cystine.^{1,2,6}

“Renal stones are also extremely common: the lifetime risk for a white man is 12–15%, and for white women it is 5–6%, with lifetime recurrence rates of up to 50%”

Familial factors may be important in a small number of cases of nephrolithiasis. Vitamin D receptor polymorphisms have been shown to be potentially important in children with stone disease, with the ApaI AA genotype being more common in such patients,⁷ whereas a variation in

the distribution of the BsmI and TaqI genotypes has been demonstrated in hypocitraturic stone formers.⁸ Variations in the start codon of the gene encoding the vitamin D receptor have been examined but found not to be of importance.⁹ The BsmI association has also been compared with bone mineral density estimates because there may be an association between renal stones and vertebral fracture, but no significant interaction could be proved.¹⁰ There is also a calcium sensing plasma membrane protein that regulates tubular reabsorption of calcium. Haplotype analysis of this CASR gene suggests that it may play a role in idiopathic hypercalciuria. The Arg990Gly polymorphism in particular may facilitate activation of CASR, thus increasing calcium excretion.¹¹ Much work remains to be done to identify common and treatable genetic causes of renal stones.

Once a patient presents with stones there is a standard sequence of investigations that is appropriate, but this paper will only deal with laboratory investigation with a view to prevention of further episodes, and will not concern itself with the management of acute episodes.

URINALYSIS

The first stage in the laboratory investigation of stones is the collection of 24 hour urine samples. Table 1 lists stone promoting and inhibiting urinary factors and those that should be assayed.^{12–16} It is also appropriate to measure serum calcium, urate, and creatinine so that creatinine clearance can be estimated as an assessment of the effectiveness of 24 hour urine collection. Various schedules for urine collection have been proposed, but most require two collections, either both of 24 hours duration or one 16 hour and one eight hour collection.¹² It is recommended that the first collection bottle should include 15–30 ml of 6M HCl, whereas the second collection should include either 20–30 ml of 0.3M sodium azide or no preservative at all.

A random urine can also be taken for the microalbumin : creatinine ratio (proximal tubular function), and if creatinine values are > 1 mg/mmol, the urine retinol binding protein : creatinine ratio should be measured.¹⁴

RENAL STONE ANALYSIS

Stone formation requires the formation of a nidus in the urinary tract, trapping of that nidus,

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Table 1 Stone promoting and stone inhibiting factors^{1 12 13 15 16}

Promoters	Inhibitors
*Calcium	Inorganic
*Sodium	*Magnesium
*Oxalate	*Pyrophosphate (assay as phosphate)
*Urate	*Citrate
*Cystine	Organic
Low urine pH	Nephrocalcin
Tamm-Horsfall protein	Tamm-Horsfall protein
*Low urine flow	Urinary prothrombin fragment 1
Bacterial products	Protease inhibitor: inter α inhibitor
	Glycosaminoglycans
	*High urine flow
Other essential urine analytes	Serum analytes
Creatinine	Calcium
Creatinine clearance	Urate
Urine albumin (microalbumin)	Creatinine
If >1 mg/mmol	Parathyroid hormone (where hypercalcaemia present)
creatinine then urine retinol binding protein	Phosphate

*Analytes that should be assessed in 24 hour urine samples of stone formers.

and accretion upon the nidus to form a crystal structure large enough to cause clinical symptoms or be detected on imaging.¹⁷ Stone analysis clearly only applies to those patients who have captured stones, either after spontaneous passage or after lithotripsy, and those who have a surgically removed stone, but many patients never have physical proof of the cause of their renal colic. For this reason, and also because stone formation is not a single phase event, analysis of stones is controversial.

"It is necessary to analyse all renal stones, because certain types of stone immediately identify appropriate treatments (for example, cystine stones)"

Calcium oxalate crystallisation is commonly found in both stone formers and non-stone formers,¹⁸ which implies that nidus formation is easy. Retention of particles may thus be the crucial factor. Calcium phosphate plaques have been found adherent to the papillary surfaces.¹⁹ Calcium phosphate is also known to increase the likelihood of supersaturated calcium oxalate solutions forming stones,¹⁷ and is frequently present in calcium oxalate stones.⁵ Therefore, it could be argued that because all calcium stones are a composite of several salts, there is no need for stones to be analysed at all.²⁰ However, this ignores the importance of other non-calcium based stones, so it is therefore necessary to analyse all renal stones,⁵ because certain types of stone immediately identify appropriate treatments (for example, cystine stones). Analysis by wet chemical qualitative methods has been shown to be too poor to be acceptable²¹: stone analysis is best carried out by x ray crystallography or infrared spectroscopy.^{12 13 21}

INTERVENTIONS AND SPECIAL TESTS

Dietary interventions

Increased fluid consumption

It has been shown that a reduction in the five year recurrence rates of nephrolithiasis can be achieved by general measures.²² Simultaneously the simplest and most difficult intervention to implement is to encourage greater fluid intake. Although it is easy to advise patients to drink more, it is often difficult for them to achieve the target of drinking sufficient to produce at least 2 litres (or 3.5 litres/day in

cystinuria) of urine daily, and longterm compliance can be a particular problem.²³ This is further complicated by the effects of heavy exercise, hot weather, and long distance travel.^{1 23} The recommendation should be to have colourless urine because yellow or brown urine is too concentrated.

Lower protein diet

The hyperfiltration theory, by which increased protein intake affects glomerular function, is well known and underpins some management regimens for chronic renal failure. Although this is difficult to evaluate in such patients, it has been tested in obese subjects during weight loss,²⁴ and high protein intake was correlated with higher glomerular filtration rates. This has been investigated further in rats and specific amino acids appear to be the mediators.²⁵ A non-animal low protein diet prevents acidosis caused by the breakdown of sulfur containing amino acids in animal protein and improves calcium homeostasis.^{1 26} In studies on Japanese stone formers, a positive correlation was found between the prevalence of nephrolithiasis and increased consumption of animal fat and protein.²⁷ Theoretically, patients with cystinuria could also benefit through a lower urine cystine load. Therefore, patients could be advised to amend their diet, but should be advised not to restrict protein intake excessively.

Low calcium diet

It used to be standard practice to advise patients to reduce/avoid dairy produce consumption to decrease their calcium intake and thus reduce their stone risk.²⁸ However, paradoxically, people who form kidney stones but have a high calcium diet are less likely than those on a low calcium diet to suffer a recurrence.²⁶ Calcium binds oxalate in the gut, preventing its absorption. Consequently, a reduction in dietary calcium can cause hyperoxaluria,²⁹ with resultant increased stone formation. It has even been suggested that the high incidence of urolithiasis in Saudi Arabia may be nutritionally mediated via poor calcium intake induced mild hyperoxaluria.³⁰ Observational studies have suggested that calcium restriction may increase stone formation and that calcium supplementation may be beneficial.^{31–33} Finally, a five year study has shown that a normal calcium intake results in a significantly lower risk of recurrence than a low calcium intake (relative risk, 0.37; 95% confidence interval, 0.18 to 0.78; $p = 0.006$).³³ Therefore, it is no longer advisable to recommend a low calcium diet for stone formers.²⁶ However, the same study³³ also found that supplementary calcium increased the risk of stone formation, so this should not be recommended either.

Low oxalate diet

In addition to hyperoxaluria caused by calcium restriction, it is also important to consider sources of excess dietary oxalate, although this can only ever result in a small reduction because only 10–15% of urine oxalate is derived from the diet.³⁴ Spinach and rhubarb represent high risk foodstuffs because they contain large quantities of bioavailable oxalate.³⁵ Nuts (almonds, hazelnuts, peanuts, pecans, and walnuts), blackcurrants, strawberries, beetroot, parsley, chives, cocoa, wheat germ, brown rice, cola, instant tea, and chocolate contain moderate amounts.^{2 35–37} The consumption of milk with tea reduces the bioavailability of oxalate.³⁸ It has been shown that a 20 fold increase in dietary oxalate can be compensated for by a very high calcium intake.³⁹ Therefore, there is little proof that severely restricting oxalate intake is beneficial, and currently it seems appropriate to advise restrictions only if there is a significant dietary excess of a particular oxalate rich nutrient.

Low sodium diet

In the dying industry, huge quantities of salt are used to encourage the precipitation of dye into cloth.⁴⁰ This salting out process also occurs in urine and will aid crystal formation. Furthermore, an increased tubular sodium load results in reduced tubular reabsorption of calcium. Every 100 mmol increase in dietary sodium increases calcium excretion by 25 mg (0.63 mmol).⁴¹ Therefore, a low sodium diet (2–3 g/day; 90–130 mmol/day) could be recommended to patients with hypercalciuria.¹ However, such a low salt diet may be unpalatable and difficult to achieve.

Increased potassium diet

It has been shown epidemiologically that there is a positive correlation between low potassium intake (< 74 mmol/day) and increased risk of stone formation.³¹ This may be the result of increased urine calcium and decreased urine citrate excretion caused by insufficient potassium intake.⁴² However, there is also an association between low potassium intake and increased sodium chloride intake in stone formers.⁴³ This may be mediated by the ion composition of processed foods, which tend to be a major source of salt in modern diets.⁴⁴

Low purine diet

Uric acid is derived from exogenous (diet) and endogenous (de novo purine synthesis and tissue catabolism) routes. Endogenous production is relatively constant at 300–400 mg/day, but the exogenous purine pool is increased by a diet rich in animal or fish protein, resulting in increased urate production. Two thirds of urate is excreted via the kidney, the remainder being lost via sweat and the bowel.⁴⁵ Evidence for dietary intervention in hyperuricosuria is limited and no longterm endpoint studies have been carried out.⁴⁶ There is therefore no clear consensus on dietary purine restriction, so moderation is probably the appropriate advice,⁶ particularly in view of the fact that low purine diets are non-palatable and compliance with them is poor.⁴⁷

Vitamin C

The effect of large doses of vitamin C in increasing urine oxalate excretion is controversial.^{48–49} It is possible that some assays convert vitamin C to oxalate, giving the false impression that high dose vitamin C increases the risk of nephrolithiasis.⁴⁹ A specific epidemiological study of vitamin intake and renal stones in women found no positive link.⁵⁰

Essential fatty acids

Greenland Eskimos and coastal Japanese are reported to have a very low incidence of renal stone disease.⁵¹ One theory to explain this “immunity” is that n-3 and n-6 polyunsaturated fatty acids affect the activity of cell membrane transporter proteins.⁵² The administration of fish oil (n-3) and evening primrose oil (n-6) has been shown to have significant effects in rat models of nephrolithiasis.^{51–52} However, it should be noted that many fish oil preparations are high in calcium and vitamin D and this may have an adverse effect. This is an area in need of further research.

Pharmacological interventions

Treatment for hypercalciuria

Hypercalciuria is defined as urine calcium excretion > 7.5 mmol/day in men or > 6.2 mmol/day in women.² There are several diuretic drugs that can affect urine calcium excretion. These include chlorothiazide, hydrochlorothiazide, and bendroflumazide (thiazide diuretics), and indapamide and chlorthalidone (diuretics closely related to thiazides). These drugs reduce hypercalciuria by increasing the fractional reabsorption of calcium in the distal nephron and decreasing intestinal calcium absorption.³⁷ There have been at least eight

prospective studies of treatment with these agents; all but two showed a reduction in recurrence rates, but the two that showed no effect were both of very short duration and therefore incapable of demonstrating clinical benefit.^{53–54} However, there were significant patient drop outs in the treatment groups, which may have caused selection biases.⁵⁴ Meta-analysis estimated the risk reduction benefit of diuretic treatment to be –21.3% (95% confidence interval, –29.2% to –13.4%) versus placebo.⁵⁵ Thus, treatment with thiazides is probably effective and worthwhile in the prevention of recurrence in patients with hypercalciuria.

Treatment for hyperoxaluria

There are no specific drugs for the reduction of production/excretion of oxalate. Oxalate absorption can be blocked by magnesium carbonate² or cholestyramine,³⁷ as described above. Magnesium can increase the solubility of calcium oxalate in vitro; therefore, it may be logical to use it to prevent stone recurrence.³⁷ The suggested dose is 650–1300 mg magnesium hydroxide/day. One randomised study has been carried out to investigate this intervention, but failed to show benefit when compared with placebo.³⁷ The final option for the treatment of hyperoxaluria is pyridoxine (vitamin B₆). Pyridoxine is the cofactor in the alanine-glyoxalate-transaminase pathway, which converts glyoxalate to glycine, and may reduce oxalate production by enzyme induction.⁵⁶ Pyridoxine supplementation is regularly used to reduce oxaluria in patients with type I and II primary hyperoxaluria.⁵⁶ An epidemiological study has shown an inverse relation between nephrolithiasis and vitamin B₆ intake (> 40 mg/day) in women.⁵⁷ Therefore, there is justification in trying to reduce oxaluria, initially with doses of 100 mg pyridoxine/day, increasing to 300 mg/day if the response is inadequate.³⁷ The dose can be titrated up to a maximum of 10 mg/kg, but the use of the minimum effective dose is recommended because high doses can cause peripheral neuropathy.⁵⁶ It should be noted that no longterm randomised trials of the effectiveness of pyridoxine for hyperoxaluria have yet been carried out.³⁷

Treatment for hyperuricosuria

Hyperuricosuria is defined as urate excretion > 4800 µmol/day in men or > 4400 µmol/day in women,⁴⁷ or a uric acid : creatinine ratio > 530 µmol/mmol. It can usefully be treated with allopurinol, a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine, and ultimately uric acid. Initially, a dose of 100–300 mg/day is used, but this may be increased to achieve reductions in urate output if necessary. Four randomised trials to evaluate the effects of treatment with allopurinol have been carried out. The outcomes were variable, with one trial⁵⁸ reporting a relative risk of stone formation for the treatment group of 0.55 after three years,^{37–59} although the others were less conclusive.^{53–54}

“Urate stones can be dissolved by urine alkalinisation, with a reported success rate of 80%”

Hyperuricosuria may also promote calcium oxalate nephrolithiasis by heterogeneous nucleation or by adsorption of macromolecular inhibitors. It may therefore be beneficial to treat hyperuricosuria to prevent calcium stone formation.

Uric acid salts are poorly soluble in acid urine. A pH of 6–7 is optimal to prevent urate stone formation.² Furthermore, urate stones can be dissolved by urine alkalinisation, with a reported success rate of 80%.⁴⁵ Urine alkalinisation is discussed below.

Urine alkalinisation/treatment for hypocitraturia

Citrate functions as a stone formation inhibitor because it reduces the supersaturation of calcium oxalate by binding to calcium and can also act by direct interference with calcium oxalate crystallisation. Hypocitraturia is found in up to 20% of stone formers and may be idiopathic or secondary to intestinal, renal, dietary, or pharmacological causes.⁶⁰ Alkalinising salts (sodium citrate, potassium citrate, potassium-magnesium citrate, sodium bicarbonate, or potassium bicarbonate) or orange juice can be used to increase urinary citrate, but only potassium citrate and potassium-magnesium citrate have been tested in randomised trials.^{37–60} Orange juice is not totally effective and potassium citrate appears to have a bone sparing effect.⁶⁰ In a three year trial of potassium citrate (30–60 mEq/day), stone formation was reduced from 1.2 to 0.1 stones/patient year, compared with no change in the placebo group.⁶¹ In a three year trial of potassium (42mEq)-magnesium (21mEq) citrate (63mEq)—potentially more effective because it supplements magnesium, which is also a stone inhibitor—12.9% of the treated group produced new stones compared with 63.6% of the placebo group.⁶² Currently, there is no consensus on whether potassium citrate or potassium-magnesium citrate is superior. Potassium salts may also assist in the replacement of potassium lost by patients on thiazides. Urine pH should be monitored because calcium phosphate precipitation occurs if the pH exceeds 7.0, and this should be avoided.

Treatment for renal tubular acidosis

Distal renal tubular acidosis is a condition that may be familial or acquired, in which the kidneys are unable to produce urine with $\text{pH} \leq 5.5$.² Autosomal dominant distal renal tubular acidosis type I has been shown to be caused by inactivating mutations of the anion exchanger 1 gene, which encodes the renal $\text{Cl}^-/\text{HCO}_3^-$ exchanger.⁶³ An autosomal recessive condition has been mapped to the gene encoding the B1 subunit of the apical proton pump (H^+ATPase) (ATP6B1).⁶³

Traditionally, distal renal tubular acidosis was tested for by giving the patient an ammonium chloride load—an unpleasant test that frequently causes nausea and vomiting. This can in most cases be replaced by a “frusemide test”, in which a standard dose of frusemide is given, which loads the proximal tubule with sodium; the renal resorption mechanisms enacted in response to this result in urine acidification and test the distal tubule effectively, but with much less patient discomfort.⁶⁴ Renal tubular acidosis is frequently associated with renal stone formation, and is often associated with low serum bicarbonate and/or potassium, and hypocitraturia. Frequently, there is an increase in phosphaturia, leading to calcium phosphate crystallisation. Patients with renal tubular acidosis respond well to treatment with effervescent potassium citrate tablets (Effercitrate: 1.5 g potassium citrate, 0.25 g citric acid; Cystopurin: 3 g potassium citrate)—which are better tolerated than sodium bicarbonate because this compound is unpalatable and causes abdominal bloating.² Furthermore, the additional sodium load from sodium bicarbonate may exacerbate hypercalciuria, and this may make potassium citrate a better treatment. Treatment is life long.

Treatment for hypomagnesuria

Magnesium is another stone formation inhibitor. Its urine concentration depends on diet, but dietary supplementation with magnesium salts may cause diarrhoea or intestinal colic and loose bowel action. Magnesium glycerophosphate, 24 mmol daily in divided doses, is better tolerated than magnesium hydroxide, but is less readily available.²

Alternatively, supplementation in conjunction with citrate may be preferable.

Treatment of cystine stones

The first cystine stone was identified in 1810 by Wollaston, who called it cystic oxide.⁶⁵ Cystinuria is an autosomal recessive disease characterised by renal and intestinal basic amino acid transport defects affecting cystine, ornithine, arginine, and lysine, of which cystine is the least soluble and therefore the most likely to precipitate as a stone.⁶⁶ Cystinuria type I has now been shown to be caused by a mutation in the gene SLC3A1 , which encodes the rBAT protein.⁶⁷ The M467T mutation appears to be particularly important, but there are several other minor variants that may also be relevant.⁶⁸ Regardless of cause, the primary goal of medical management is to prevent the formation of new stones by reducing the cystine concentration to below its upper limit of solubility. The precise solubility limits are unclear, with a variety of possibilities cited: urine solubility of 250 mg/litre (200 $\mu\text{mol/litre}$) at pH 5.0, rising to 500 mg/litre (410 $\mu\text{mol/litre}$) at pH 7.5, and 1000 mg/litre (820 $\mu\text{mol/litre}$) at pH 8.0^{69–70}; 240–480 mg/litre (200–400 $\mu\text{mol/litre}$)⁷¹; or an upper limit in physiological urine conditions of 300 mg/litre (250 $\mu\text{mol/litre}$).⁶² It has a known solubility in water of 110 mg/litre (90 $\mu\text{mol/litre}$) at 25°C and 520 mg/litre (430 $\mu\text{mol/litre}$) at 75°C.⁷² Alternatively, reduced stone formation can be achieved by increasing the solubility of cystine by urine alkalinisation with potassium citrate (see above) (ideally to $\text{pH} > 7.5$, but this is difficult and impractical so usually a target of > 6.5 is applied) or chelation. Usually, however, chelation alone is sufficient to prevent further stone formation.⁶⁶ In addition, protein restriction will reduce the cystine load. Available chelating agents include:

- (1) D-Penicillamine, which produces cysteine–penicillamine heterodimers that are 50 times more soluble than cysteine–cysteine (cystine) homodimers. The average dose used is 600–1200 mg/day. D-Penicillamine causes a wide variety of side effects, including gastrointestinal disturbances, allergic reactions, arthralgia, leucopenia, thrombocytopenia, proteinuria, and nephritic syndrome.⁶⁶ Furthermore, longterm treatment may result in vitamin B₆ deficiency, so that prophylaxis with B₆ (50 mg/day) is advisable.⁷³
- (2) α Mercaptopropionylglycine (Tiopronin), which is a second generation chelating agent that has a similar mode of action to penicillamine but fewer side effects. This drug should be started at 250 mg/day and titrated according to urine cystine, increasing to 800 mg/day or 1200 mg/day.⁶⁶ Tiopronin is available on a named patient basis in the UK.
- (3) Bucillamine, which is a third generation chelating agent that is theoretically superior to penicillamine, although experience with this drug is limited.⁶⁶

The monitoring of treatment for cystinuria should include the quantitative assessment of cystine output and may include assessment of fractional cystine clearance, but it is also advisable to check for side effects, including tests for proteinuria and a regular full blood count.²

Treatment for recurrent infection

Magnesium ammonium phosphate stones occur when there is recurrent infection with urease positive organisms—that is, most proteus and providentia species and some forms of *Klebsiella pneumoniae* and *Serratia marcescens*.⁶ Urease releases NH_4^+ ions, which neutralise H^+ and render the urine pH more alkaline. Consequently, NH_3 hydrolyses to NH_4OH , releasing more NH_4^+ , CO_2 is converted to HCO_3^- and thence to CO_3^{2-} , and any phosphate present becomes deprotonated to PO_4^{3-} .

This chain of events leads to the precipitation of $\text{MgNH}_4\text{PO}_4 \cdot \text{H}_2\text{O}$ (struvite) and $\text{Ca}_{10}[\text{PO}_4]_6\text{CO}_3$ (calcium apatite) stones, which requires a pH greater than 7.2.^{6, 74} Surgical stone removal is difficult and any retained fragments will contain bacteria that will start creation of a new stone.⁶ It is possible to try to prevent recurrent infection by chronic antibiotic treatment, but this may only slow progression rather than be curative.⁶ Furthermore, antibiotic induced reduction in intestinal *Oxalabacter formigenes* (which normally destroys intestinal oxalate) activity may increase renal stone risk.⁷⁴ Another possible treatment is a urease inhibitor. Acetohydroxamic acid has been shown to be effective in rat pyelonephritis models and in a small human study, but its use is severely limited by side effects.^{37, 75} Further research continues.

Secondary nephrolithiasis: treatment of underlying causes

Hypercalcaemia

An increased risk of renal stone formation occurs in hypercalcaemic conditions, such as hyperparathyroidism, hyperthyroidism, sarcoidosis, immobilisation, and milk alkali syndrome.¹³ Clearly, if any of these conditions are identified, the initial aim is to treat the primary cause of the hypercalcaemia and reinvestigate for stone risk after such treatment is satisfactory.

Inflammatory intestinal disease

Patients with chronic diarrhoeal illnesses such as ulcerative colitis and Crohn's disease can develop enteric hyperoxaluria, which results in an increased risk of developing renal stones.^{2, 36} Stones have been shown to develop in 3.2–8.6% of patients with inflammatory bowel disease—a rate at least twice as high as in people with a normal bowel.³⁶ It is often thought that oxalate is the primary problem in these patients because excess oxalate is absorbed through the inflamed bowel wall, as accentuated by the inability of these patients to tolerate appreciable amounts of vegetable matter in their diet. However, up to 29% of stones identified in a series of these patients were uric acid, compared with 5–10% in idiopathic stone disease.³⁶ Urate stones are particularly common in patients after colectomy. A further problem for this class of patient is urine supersaturation. Many restrict their fluid intake to control diarrhoea and consequently have lower urine volumes.³⁶ Furthermore, ileostomy can have similar effects. Finally, patients with ileostomy tend to produce acid urine as a result of the loss of alkaline ileostomy fluid.

“Urate stones are particularly common in patients after colectomy”

There are no controlled trials of renal stone prevention in patients with ileostomy or colitis.³⁶ Those with a low urine volume should be advised to try to consume more fluid. Treatment of enteric hyperoxaluria may be with calcium carbonate,² or with cholestyramine, an anionic exchange resin that combines with bile acids to prevent their absorption.³⁷ Both agents combine with oxalate in the gut and render it unavailable for absorption. The required dose should be identified by titration against urine oxalate measurements. Uric acid stones can be treated with urine alkalinisation with sodium bicarbonate or potassium citrate, and by allopurinol.³⁶

Rare causes of nephrolithiasis

Primary hyperoxaluria

This is a rare autosomal recessive condition in which hyperoxaluria results from disturbances in the oxalate

biosynthetic pathway.⁷¹ Type I hyperoxaluria is caused by reduced hepatic peroxisomal alanine glyoxalate aminotransferase,⁷⁶ which results in increased availability of glyoxalate for conversion to oxalate. Other forms of the disease include a deficiency of transfer of active alanine glyoxalate aminotransferase to microsomes or a reduction in its activity. The transfer failure form of primary hyperoxaluria has been shown to be the result of a synergistic interaction between a common P11L (Pro→Leu) polymorphism and a disease specific G170R mutation, which generates a functionally weak mitochondrial targeting sequence.^{77, 78} All forms lead to very high oxalate excretion (1–3 mmol/day). Stone formation begins in childhood and tubulointerstitial nephropathy progresses to chronic renal failure.^{79, 80} Treatment with pyridoxine lowers oxalate production in some patients,⁷⁹ but others have received liver transplantation to replace the missing enzyme.⁸⁰

X linked nephrolithiasis (Dent's disease)

There have been four independent descriptions of X linked nephrolithiasis syndromes, which have all been shown to be caused by mutations in the voltage gated chloride channel gene *CLCN5*.^{63, 81} The chloride channel 5 protein has been localised to the cells of the proximal tubule and intercalated cells of the cortical collecting duct. Results from knockout mouse models have not been entirely conclusive, but it appears that the mutation causes a renal calcium leak, leading to hypercalciuria, and thence renal stone formation.⁶³ There is as yet no evidence that this is a numerically important cause of renal stones, but it may indicate that in the future more detailed pedigree tracing of patients with nephrolithiasis would be appropriate. Diagnosis is usually made by measuring urine microalbumin and, if creatinine is > 1 mg/mmol, then assaying for retinol binding protein.¹⁴

2,8-Dihydroxyadenine stones

Approximately one in 1000 stone formers has an autosomal recessive deficiency of adenine phosphoribosyl transferase, which is necessary for purine metabolism, and which can be diagnosed from enzyme analysis in red blood cells. Adenine acts as a substrate for xanthine oxidase, which catalyses its conversion to 2,8-dihydroxyadenine, which appears in excess in urine resulting in stone formation. Treatment is with allopurinol.²

FOR DEBATE

The above strategy depends on the careful evaluation of urine metabolic profiles with monitoring to identify whether drug treatment has been effective. It has been proposed that this should be abandoned because studies in unstratified patients have shown that successful prophylaxis against renal stones can be achieved simply by treating every patient with potassium citrate, with great savings of time and laboratory investigations.⁵⁹ Although this has some superficial attractions, this may lead to the inadequate treatment of some patients, especially those with cystinuria, and may also in the longterm lead to an increase in calcium phosphate stones if there is no monitoring of urine pH. Furthermore, although placebo controlled trials have shown a clear benefit of potassium citrate supplementation in patients known to be hypocitraturic,⁸² this does not suggest that the treatment of all patients in the same way will be effective. Until properly constituted longterm randomised preventative trials can be carried out, it therefore seems logical to continue in the attempt to target treatment to the clinical abnormality, and consequently to continue laboratory investigation before treatment.

REFERENCES

- 1 Bihl G, Meyers A. Recurrent renal stone disease—advances in pathogenesis and clinical management. *Lancet* 2001;**358**:651–6.
- 2 Wilkinson H. Clinical investigation and management of patients with renal stones. *Ann Clin Biochem* 2001;**38**:180–7.
- 3 Pantanowitz D, Pollen J, Politzer WM. Urinary calculi. *S Afr Med J* 1973;**43**:128–31.
- 4 Meyers AM, Whalley N, Martins M. Diagnostic and therapeutic aspects of recurrent renal stones disease. *African Journal of Nephrology* 1998;**2**:12–17.
- 5 Daudon M, Donsimoni R, Hennequin C, et al. Sex- and age-related composition of 10617 calculi analysed by infrared spectroscopy. *Urol Res* 1995;**23**:319–26.
- 6 Bushinsky DA. Kidney stones. *Adv Intern Med* 2001;**47**:219–38.
- 7 Ozkaya O, Soylemezoglu O, Misirlioglu M, et al. Polymorphisms in the vitamin D receptor gene and the risk of calcium nephrolithiasis in children. *Eur Urol* 2003;**44**:150–4.
- 8 Mossetti G, Vuotto P, Rendina D, et al. Association between vitamin D receptor gene polymorphisms and tubular citrate handling in calcium nephrolithiasis. *J Intern Med* 2003;**253**:194–200.
- 9 Vezzoli G, Soldati L, Proverbio MC, et al. Polymorphism of vitamin D receptor gene start codon in patients with calcium kidney stones. *J Nephrol* 2002;**15**:158–64.
- 10 Heilberg IP, Teixeira SH, Martini LA, et al. Vitamin D receptor gene polymorphism and bone mineral density in hypercalciuric calcium-stone-forming patients. *Nephron* 2002;**90**:51–7.
- 11 Vezzoli G, Tanini A, Ferrucci L, et al. Influence of calcium-sensing receptor gene on urinary calcium excretion in stone-forming patients. *J Am Soc Nephrol* 2002;**13**:2517–23.
- 12 Tiselius HG, Ackerman D, Alken P, et al. EAU guidelines: guidelines on urolithiasis. *Eur Urol* 2001;**40**:362–71.
- 13 Tiselius H-G. Medical evaluation of nephrolithiasis. *Endocrinol Metab Clin North Am* 2002;**31**:1031–50.
- 14 Norden AG, Scheinman SJ, Deschodt-Lanckman MM, et al. Tubular proteinuria defined by a study of Dent's (CLCN5 mutation) and other tubular diseases. *Kidney Int* 2000;**57**:240–9.
- 15 Whalley N, Martins M, Wandy KRC, et al. Lithogenic risk factors in normal black volunteers, and black and white recurrent stone formers. *BJU Int* 1999;**84**:243–8.
- 16 Worcester EM. Inhibitors of stone formation. *Semin Nephrol* 1996;**16**:474–86.
- 17 Smith CL. Renal stone analysis: is there any clinical value? *Curr Opin Nephrol Hypertens* 1998;**7**:703–9.
- 18 Robertson WG, Peacock M. Calcium crystalluria in recurrent renal stone formers. *Lancet* 1969;**2**:21–4.
- 19 Randall A. Papillary pathology as a precursor of primary renal calculus. *J Urol* 1940;**44**:580–9.
- 20 Henderson MJ. Stone analysis is not useful in the routine investigation of renal stone disease. *Ann Clin Biochem* 1995;**32**:109–11.
- 21 Kasidas GP, Samuell CT, Weir TB. Renal stone analysis: why and how? *Ann Clin Biochem* 2004;**41**:91–7.
- 22 Hoskins DH, Erickson SB, Vandenburg CJ. The stone clinic effect in patients with idiopathic calcium urolithiasis. *J Urol* 1983;**130**:1115–18.
- 23 Borghi L, Meschi T, Schianchi T, et al. Urine volume: stone risk factor and preventive measure. *Nephron* 1999;**81**(suppl):31–7.
- 24 Skov AR, Toubro S, Bulow J, et al. Changes in renal function during weight loss induced by high vs. low-protein low-fat diets in overweight subjects. *Int J Obes Relat Metab Disorder* 1999;**23**:1170–7.
- 25 Colina VL, Perez-Gonzalez M, Villalobos J, et al. Effect of hypoproteic diets enriched with essential and non-essential amino acids on the uninephrectomized rat. *Acta Cient Venez* 2002;**53**:21–8.
- 26 Martini LA, Heilberg IP. Stop dietary calcium restriction in kidney stone-forming patients. *Nutr Rev* 2002;**60**:212–14.
- 27 Iguchi M, Kataoka K, Kohri K, et al. Nutritional risk factors in calcium stone disease in Japan. *Urol Int* 1984;**39**:32–5.
- 28 Heller HJ. The role of calcium in the prevention of kidney stones. *J Am Coll Nutr* 1999;**18**:373S–8S.
- 29 Messa P, Marangella M, Paganin L, et al. Different dietary calcium intake and relative supersaturation of calcium oxalate in the urine of patients forming renal stones. *Clin Sci* 1997;**93**:257–63.
- 30 Robertson WG, Hughes H. Importance of mild hyperoxaluria in the pathogenesis of urolithiasis: new evidence from studies in the Arabian peninsula. *Scanning Microsc* 1993;**7**:391–4.
- 31 Curhan GC, Willett WC, Rimm EB, et al. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993;**328**:833–8.
- 32 Curhan GC, Willett WC, Speizer FE, et al. Comparison of dietary calcium with supplementary calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med* 1997;**126**:497–504.
- 33 Borghi L, Schianchi T, Meschi T, et al. Comparison of two diets for the prevention of recurrent renal stones in idiopathic hypercalciuria. *N Engl J Med* 2002;**346**:77–84.
- 34 Hess B. Low calcium diet in hypercalciuric calcium nephrolithiasis patients: first do no harm. *Scanning Microsc* 1996;**10**:547–54.
- 35 Brinkley LJ, Gregory J, Pak CYC. A further study of oxalate bioavailability in foods. *J Urol* 1990;**144**:94–6.
- 36 Worcester EM. Stones from bowel disease. *Endocrinol Metab Clin North Am* 2002;**31**:979–99.
- 37 Borghi L, Meschi T, Schianchi T, et al. Medical treatment of nephrolithiasis. *Endocrinol Metab Clin North Am* 2002;**31**:1051–64.
- 38 Savage GP, Charrier MJ, Vanhanen L. Bioavailability of soluble oxalate from tea and the effect of consuming milk with the tea. *Eur J Clin Nutr* 2003;**57**:415–19.
- 39 Hess B, Jost C, Zipperle L, et al. High calcium intake abolishes hyperoxaluria and reduces urinary crystallization during a 20-fold normal oxalate load in humans. *Nephrol Dial Transplant* 1998;**13**:2241–7.
- 40 Heath D, Slocum MS, Clapp TG. Addressing salt issues in textile dyeing using an ISQ and ARIZ. <http://www.triz-journal.com/archives/2000/01/d/> (last accessed 02/02/04).
- 41 Lemann J, Adams ND, Gray RW. Urinary calcium excretion in human beings. *N Engl J Med* 1979;**301**:535–41.
- 42 Lemann J, Pleuss JA, Gray RW, et al. Potassium administration reduces and potassium deprivation increases urinary calcium excretion in healthy adults. *Kidney Int* 1991;**39**:973–83.
- 43 Borsatti A. Calcium oxalate nephrolithiasis: defective oxalate transport. *Kidney Int* 1991;**39**:1283–98.
- 44 <http://www.foodstandards.gov.uk/healthierating/dailydiet/salt/> (last accessed 02/01/04).
- 45 Shekarri B, Stoller M. Uric acid nephrolithiasis: current concepts and controversies. *J Urol* 2002;**168**:1307–14.
- 46 Hess B. Nutritional aspects of stone disease. *Endocrinol Metab Clin North Am* 2002;**31**:1017–30.
- 47 Sorensen CM, Chandhoke PS. Hyperuricosuric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002;**31**:915–25.
- 48 Hughes C, Dutton S, Trusell A. High intakes of ascorbic acid and urinary oxalate. *J Hum Nutr* 1981;**35**:272–80.
- 49 Wandzilak T, D'Andre S, Davis P, et al. Effect of high dose of vitamin C on urinary oxalate levels. *J Urol* 1994;**151**:834–7.
- 50 Curhan GC, Willett WC, Speizer FE, et al. Intake of vitamin B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999;**10**:840–5.
- 51 Burgess NA, Reynolds TM, Williams N, et al. Evaluation of four animal models of intrarenal calcium deposition and assessment of the influence of dietary supplementation with essential fatty acids on calcification. *Urol Res* 1995;**23**:239–42.
- 52 Baggio B. Genetic and dietary factors in idiopathic calcium nephrolithiasis. What do we have, what do we need? *J Nephrol* 1999;**12**:371–4.
- 53 Pearle MS. Prevention of nephrolithiasis. *Curr Opin Nephrol Hypertens* 2001;**10**:203–9.
- 54 Ackermann DK. Prospective therapeutic studies in nephrolithiasis. *World J Urol* 1997;**15**:172–5.
- 55 Pearle MS, Roehrborn CG, Pak CY. Meta-analysis of randomised trials for medical prevention of calcium oxalate nephrolithiasis. *J Endourol* 1999;**13**:679–85.
- 56 Asplin JR. Hyperoxaluric calcium nephrolithiasis. *Endocrinol Metab Clin North Am* 2002;**31**:927–49.
- 57 Gurhan GC, Willett WC, Speizer FE, et al. Intake of vitamins B6 and C and the risk of kidney stones in women. *J Am Soc Nephrol* 1999;**10**:840–5.
- 58 Ettinger B, Tang A, Citron JT, et al. Randomized trial of allopurinol in the prevention of calcium oxalate calculi. *N Engl J Med* 1986;**27**:1386–9.
- 59 Pak CYC. Medical prevention of renal stone disease. *Nephron* 1999;**81**(suppl):60–5.
- 60 Pak CYC. Citrate and renal calculi: an update. *Miner Electrolyte Metab* 1994;**20**:371–7.
- 61 Barcelo P, Wuhl O, Servitge E, et al. Randomized double-blind study of potassium citrate in idiopathic hypocitraturic calcium nephrolithiasis. *J Urol* 1993;**150**:1761–4.
- 62 Ettinger B, Pak CYC, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997;**158**:2069–73.
- 63 Zerwech JE, Reed-Gitomer BY, Pak CYC. Pathogenesis of hypercalciuric nephrolithiasis. *Endocrinol Metab Clin North Am* 2002;**31**:869–84.
- 64 Reynolds T, Burgess N, Matanhela S, et al. The frusemide test: a simple screening test for urinary acidification defect in urolithiasis. *Br J Urol* 1993;**72**:153–6.
- 65 Wollaston WH. On cystic oxide: a new species of urinary calculus. *Transactions of the Royal Society London* 1810;**100**:223–30.
- 66 Shekarri B, Stoller ML. Cystinuria and other noncalcareous calculi. *Endocrinol Metab Clin North Am* 2002;**31**:951–77.
- 67 Calonge MJ, Gasparini P, Chillaron J, et al. Cystinuria caused by mutations in rBAT, a gene involved in the transport of cystine. *Nat Genet* 1994;**6**:420–5.
- 68 Guillen M, Corella D, Cabello ML, et al. Association between M467T and 114 C→A variants within the SLC3A1 gene and some phenotypical traits in cystinuria patients from Spain. *Hum Genet* 2000;**106**:314–20.
- 69 Reminger GM. Renal calculi: pathogenesis, diagnosis and medical therapy. *Semin Nephrol* 1992;**12**:200–16.
- 70 Wilson DM. Clinical and laboratory evaluation of renal stone patients. *Endocrinol Metab Clin North Am* 1990;**19**:773–803.
- 71 Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. *N Engl J Med* 1992;**327**:1141–52.
- 72 Hodgman CD, Weast RC, Selby SM. *Handbook of chemistry and physics*, 40th ed. Cleveland Ohio: Chemical Rubber Publishing Co, 1958.
- 73 Milliner DS. Cystinuria. *Endocrinol Metab Clin North Am* 1990;**19**:889–907.
- 74 Abrahams HM, Stoller ML. Infection and urinary stones. *Curr Opin Urol* 2003;**13**:63–7.
- 75 Rodman JS. Struvite stones. *Nephron* 1999;**81**(suppl 1):50–9.
- 76 Scheinman JL. Primary hyperoxaluria: therapeutic strategies for the 90s. *Kidney Int* 1991;**40**:389–99.

- 77 **Lumb MJ**, Birdsey GM, Danpure CJ. Correction of an enzyme trafficking defect in hereditary kidney stone disease in vitro. *Biochem J* 2003;**374**:79–87.
- 78 **Danpure CJ**, Lumb MJ, Birdsey GM, *et al*. Alanine:glyoxalate aminotransferase peroxisome-to-mitochondrion mistargeting in human hereditary kidney stone disease. *Biochim Biophys Acta* 2003;**1647**:70–5.
- 79 **Yendt ER**, Cohan M. Response to a physiologic dose of pyridoxine in type-I hyperoxaluria. *N Engl J Med* 1985;**315**:1386–9.
- 80 **Watts RWE**, Morgan SH, Danpure CL, *et al*. Combined hepatic and renal transplantation in primary hyperoxaluria type-I: clinical report of nine cases. *Am J Med* 1991;**90**:179–88.
- 81 **Schieneman SJ**. X-linked hypercalciuric nephrolithiasis: clinical syndromes and chloride channel mutations. *Kidney Int* 1998;**53**:3–17.
- 82 **Heilberg IP**. Update on recommendations and medical treatment of renal stone disease. *Nephrol Dial Transpl* 2000;**15**:117–23.

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