Review Article

Hyperoxaluria and renal calculi

Robin G. Woolfson and Martin A. Mansell

Division of Nephrology, St Peter's Institute of Urology and Nephrology, Middlesex Hospital, Mortimer Street, London W1N 8AA, UK

Introduction

Many Western countries are experiencing an epidemic of renal calculi, causing immediate problems with acute pain and morbidity together with worries for the future because of the likelihood of recurrent stone formation. Renal or ureteric colic is the commonest surgical admission diagnosis in this country and it has been suggested that up to 12 million Americans will suffer a stone episode during their lifetime.¹ Because of the scale of the clinical problem presented by renal colic, immediate and short-term management dominates the discussion with rather less attention paid to analysis of the factors involved in stone formation and prevention of recurrence. In view of the substantial costs of the treatment of kidney stones (\$2 billion in 1986 in the USA alone²), this focus may not be altogether appropriate.

Most upper tract stones are composed of calcium oxalate and the definition of 'idiopathic hypercalciuria' some 60 years ago has tended to emphasize the importance of increased urinary calcium excretion in their aetiology. However, in the last 10–15 years, it has become clear that quite small changes in urinary oxalate levels may have profound effects on the likelihood of calcium oxalate crystal formation and subsequent urolithiasis.³ The current interest in hyperoxaluria and its pathophysiology results from the development of accurate methods of measuring oxalate in blood and urine^{4,5} and advances in our understanding of the physical processes involved in urinary crystal formation.⁶ We review some current thinking on oxalate and renal calculi; a number of excellent recent reviews on the broader aspects of urolithiasis are also available.^{1,7–9}

Biochemistry of oxalate

Oxalic acid is a strong dicarboxylic acid present as oxalate in plasma at 1–3 $\mu\text{mol/l}$ and excreted in the

urine at about 0.2–0.4 mmol/24 h. The solubility of oxalate in water is only about 50 $\mu\text{mol/l}$ so that the importance of naturally occurring inhibitors of crystallization in urine, such as citrate and nephrocalcin, is obvious. A typical diet contains 1–2 mmol oxalate per day, of which more than 95% is precipitated in the gut lumen and excreted in the form of insoluble calcium salts. Thus the absorption of oxalate from the gut lumen may depend on the adequacy of the dietary intake of calcium.¹⁰ Most urinary oxalate is derived from endogenous metabolism, although heavy consumption of oxalate rich foods such as nuts, chocolate, tea or spinach can introduce an important dietary component to hyperoxaluria, but this is unusual. The metabolism of glyoxylate and glycine gives rise to oxalate, with lesser amounts coming from hydroxyproline, other amino acids and sugars. Although ascorbic acid is also a precursor it seems that this route is fairly limited, because the consumption of mega doses of vitamin C (5–10 g per day) causes only mild hyperoxaluria.

Oxalate is a metabolic end product, the excretion of which is made entirely via the urine, apart from some possible intestinal excretion of trivial degree. It is not significantly protein bound so that it is freely filtered at the glomerulus; additional secretion occurs in the tubule so that, in normal individuals, oxalate clearance may be 50–100% greater than that of creatinine.¹¹ Sixty per cent of urinary oxalate forms a soluble complex with sodium with the remainder forming a variety of less soluble calcium complexes.

Factors in crystal formation

Normal urine is supersaturated with respect to many of its constituents such as oxalate, calcium, urate, phosphate, etc. All urine contains a variety of inhibitors of crystallization, of which the most important include citrate, nephrocalcin, Tamm–Horsfall protein, magnesium and glycosaminoglycans. Obviously, other factors such

as urine pH, concentration and volume can have major effects on other crystal-forming systems such as urate, calcium phosphate and cystine in addition to the absolute concentrations of these various chemical constituents. Crystal formation is a complex, dynamic physical process that occurs when a variety of factors that favour precipitation of insoluble complexes dominate the inhibitors that will favour their dissolution. These various processes can be examined by computer simulation and show, for example, that for calcium oxalate crystallization small changes in oxalate concentrations are very much more important than larger increases in calcium concentration.¹²

About half of all patients presenting with calcium oxalate calculi will be found to have idiopathic hypercalciuria; this diagnosis implies that hypercalcaemia and other disorders of calcium metabolism have been excluded and probably reflects either an increased renal tubular leak of calcium or elevated calcium absorption from the intestine.¹³ In-patients with idiopathic hypercalciuria, stone growth and new stone formation can be improved by measures that reduce urinary calcium excretion such as dietary restriction, thiazide diuretics or cellulose phosphate.

It is common to find hypocitraturia in patients with calcium oxalate calculi, although this requires a specialist laboratory; urine citrate varies with pH and the normal ranges for men and women are very different. Citrate is the most important inhibitor of calcium oxalate crystal formation in normal urine because it forms soluble complexes with free calcium ions.¹⁴ Low urine citrate levels are associated, for example, with a high animal protein intake, thiazide-induced hypokalaemia and volume depletion and can be increased by oral alkali supplements. Oral potassium citrate is widely used in the USA, and has been shown to reduce the likelihood of stone growth and recurrence.

Alkali administration, as well as increasing urinary citrate, will also correct the very acid urine (pH less than 5.5) found in about 25% of stone formers. An acid urine will tend to promote uric acid crystallization that can act as a nidus for calcium oxalate crystals (epitaxy) and also bind macromolecular inhibitors.⁶ Low urine pH may be associated with relative oliguria or chronic diarrhoea, and will aggravate the risks of crystallization associated with the hyperuricosuria that is present in about 20% of patients with calcium oxalate stones.

Causes of hyperoxaluria

A complete list of the possible causes of hyperoxaluria is given in Table I, although only those

Table I Causes of hyperoxaluria

Primary hyperoxaluria
Type 1 (PH1)
Type 2 (PH2)
Mild metabolic hyperoxaluria (PH3)
Secondary hyperoxaluria
Increased oxalate absorption – 'enteric hyperoxaluria'
Small bowel disease, for example, Crohn's disease, jejunio-ileal bypass
Pancreatic failure
Increased endogenous oxalate synthesis
Pyridoxine deficiency
Excess oxalate or precursor intake
Oxalate (dietary)
Ascorbic acid
Glycine (post-prostatectomy irrigation)
Ethylene glycol
Methoxyflurane

associated with renal calculi will be considered further.

Primary hyperoxaluria

Two types have been described and both are very rare:¹⁵ there are perhaps 150 reports of Type I cases and 18 reports of Type II. Type I (PH1) is an autosomal recessive disease associated with dramatic hyperoxaluria (up to 8 mmol per day) and hyperglycollic aciduria. Patients present in infancy or childhood with recurrent calcium oxalate nephrolithiasis causing obstruction, infection and progressive renal impairment. Oxalate retention accelerates as renal function declines and leads to the development of systemic oxalosis; oxalate deposition in various tissues can lead to heart block, peripheral gangrene and crippling bone disease. The disease is due to a deficiency of the hepatic peroxisomal enzyme alanine glyoxylate aminotransferase (AGT), which is responsible for the conversion of glyoxylate, the immediate precursor of oxalate, to glycine. AGT is pyridoxine dependent and about 30% of patients respond to large doses of vitamin B₆ (400–800 mg per day) with a useful reduction in the intensity of their hyperoxaluria. The enzyme may be absent, catalytically inactive or wrongly localized to the hepatic mitochondria; in all cases hyperoxaluria results from the increased levels of glyoxylate. Once these patients have developed end-stage renal failure, life expectancy on regular dialysis is limited, because of the progression of systemic oxalosis. Similarly, the lifespan of renal transplants is limited because of the continuing hyperoxaluria and the risks of renal oxalosis and calculus formation. The definitive treatment is a combined synchronous hepato-renal transplant, with removal of

the native liver;¹⁶ this corrects the enzyme deficiency and restores renal function.

PH2 is very rare indeed and is due to deficiency of D-glycerate dehydrogenase.^{17,18} The disease probably results because this is the same enzyme as glyoxylate reductase and its deficiency would be expected to increase glyoxylate levels. The enzyme is probably widely distributed, unlike AGT, and the disease seems to be milder than PH1, with only two cases of end-stage renal failure described. Data on the effectiveness of renal transplantation in this condition are very limited.

Mild metabolic hyperoxaluria

About 20% of patients with calcium oxalate calculi are found to have mild hyperoxaluria, with urine values of 0.4–0.6 mmol per day. The reason for this is unclear, although occasionally a dietary component can be identified and corrected. Urinary glycollate levels are normal so that a mild variant of PH1 can be excluded. It seems likely that some patients do have truly enhanced endogenous oxalate production or increased absorption of dietary oxalate,¹⁹ combined in some cases with reduced urinary clearance so that plasma oxalate levels may be elevated. These patients tend to have normal urinary levels of calcium and citrate, although hyperuricosuria may be associated. Typically, the response to pyridoxine supplementation is either absent or short-lived and the exact biochemical abnormality in these patients has yet to be defined.

Enteric hyperoxaluria

Hyperoxaluria and renal calculus formation commonly occur in a range of gastrointestinal disorders characterized by steatorrhoea such as Crohn's disease, jejunio-ileal bypass for obesity and pancreatic failure.²⁰ Dietary calcium is bound by the steatorrhoea so that there is less calcium available to complex dietary oxalate, more of which is thus available for absorption in the colon. An additional factor is that deconjugated bile salts have toxic effects on the colonic mucosa so that oxalate absorption may be directly enhanced. In such patients the degree of hyperoxaluria may range up to 0.8–1 mmol per day and the formation of renal calculi is a very real problem; in patients who have undergone jejunio-ileal bypass for morbid obesity, renal calculi occur in about 30% and uncontrollable hyperoxaluria may be an indication for reversal of the operation in about 10%. Patients with steatorrhoea commonly show other urinary abnormalities that predispose to stone formation such as relative oliguria, hyperuricosuria, acid

urine and low levels of urinary inhibitors. Management of enteric hyperoxaluria may be very difficult and involves increasing the luminal calcium concentration with supplements of calcium carbonate, dietary restriction of fat and oxalate together with treatment, if possible, of the underlying cause.²¹

Conclusion

In this country, at least, the metabolic investigation of patients with recurrent renal calculi has not attracted the attention it deserves. This is partly because of the improved techniques for stone removal, such as lithotripsy and percutaneous nephrolithotomy and partly because of the immense clinical load represented by this group of patients. A comprehensive metabolic screen (Table II) in stone-forming patients involves a variety of relatively simple tests on blood and urine that should be within the scope of all hospital laboratories. The experience is that, when these tests are done, one or more abnormalities will be detected that are amenable to various therapeutic measures, with a greatly reduced risk of recurrent stone formation. It is likely that the role of oxalate in calcium stone formation will be recognized to be of increasing importance now that accurate methods of measurement have become available.

Table II Routine metabolic screen

A routine metabolic screen should be conducted to identify risk factors for urolithiasis:

Blood tests

Haematology and full biochemistry, including:

Bicarbonate
Calcium
Phosphate
Uric acid

Spot urine

Mid-stream urine specimen for:

Microscopy
Culture and sensitivity
pH
Cystine screen

24-hour urine collection

Volume
pH
Calcium
Oxalate
Urate
Citrate
Magnesium
Phosphate

Stone analysis

Both quantitative and qualitative

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