Renal stone disease

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Abstract

Renal stone disease (urolithiasis, nephrolithiasis) covers many conditions causing kidney, ureteric or bladder stones. These include metabolic and inherited disorders, anatomical defects of the upper or lower urinary tract, and chronic urinary infection. However, most cases of renal stones are idiopathic. They present with loin or abdominal pain, and visible or non-visible haematuria; this is followed by eventual passage of a stone and resolution or the need for further investigation and intervention. Renal stones often recur and it is important to identify the underlying cause, particularly as stones can be related to diet and lifestyle, and are often associated with hypertension or diabetes mellitus. Although clinical management is largely surgical and can seem simple, the increasing prevalence of renal stone disease in developed countries is becoming a significant economic and health burden.

Keywords Calcium oxalate; calcium phosphate; cystine; diet; infection; metabolic screening; MRCP; stones; uric acid

Key points

- Renal stone disease is increasingly common
- It is characterized by relatively high recurrence rates
- Genetics and dietary factors play a role in pathogenesis
- A detailed investigation of blood and urine as well as dietary habits is central to the diagnosis and treatment of renal stone disease
- Dietary changes, increased fluid intake and selected drugs such as thiazides, citrate and allopurinol are effective in reducing the risk of recurrence

Prevalence and epidemiology

Renal stone disease is common; in the UK about 8% of men and around 4% of women form at least one stone by the end of their sixth decade. It is more common in affluent, industrialized countries than in poorer countries with agrarian economies. The prevalence is rising in most countries.

Populations that consume diets rich in animal protein (meat, fish, poultry) have a higher risk of stones than those with a more vegetarian diet. The risk of forming a stone is further increased by a high intake of refined sugar, high salt (which increases urinary calcium excretion) and inadequate intake of calcium. A low fluid intake, with or without a high ambient temperature, increases the risk of forming stones by increasing the concentration of stone-forming salts and acids in the urine. Stone formation tends to recur: without preventive measures after a first stone, about 35% of individuals return within 5 years with at least one further stone.[1]

A positive family history of kidney stones is also an important risk factor; it is present in up to 50% of stone-formers, and first-degree relatives of stone-formers are twice as likely to have or develop a stone. A strong genetic influence on the excretion of calcium, oxalate, uric acid and citrate is very likely. Several genes have been implicated or investigated as possible contributors to 'idiopathic' kidney stone risk. Monogenic causes are relatively rare, although it has recently been suggested that they could represent up to 15% of all kidney stones.[2]

Kidney stone disease is associated with systemic conditions such as diabetes mellitus, high blood pressure, chronic kidney disease and cardiovascular disease.

Pathophysiology of stone formation

The salts and acids that normally crystallize in kidney stones do so because of their relative insolubility in urine. The most insoluble is calcium oxalate; once a calcium oxalate stone is trapped in the urinary tract, it is almost impossible for it to redissolve. Its solubility is independent of urinary pH, unlike the solubilities of other common stone constituents such as cystine and uric acid (soluble in alkali) or calcium phosphate and magnesium ammonium phosphate (soluble in acid). However, the latter occurs only in the presence of infection involving a urea-splitting bacterium that produces high levels of ammonia (and ammonium ions) and an alkaline environment.

The various urinary risk factors associated with stone formation are shown in Figure 1. For calcium-containing stones, the risk factors are a low urine volume, raised urine pH (>6.2), hypercalciuria, hyperoxaluria, hyperuricosuria, hypocitraturia (Table 1) and low urinary magnesium excretion.[3]

Clinical presentation

Symptoms and signs

Presentation can vary from asymptomatic — detected incidentally on a plain X-ray, ultrasound or computed tomography (CT) scan requested for another reason — to intensely painful with typical and localizing renal or ureteric colic, back or abdominal

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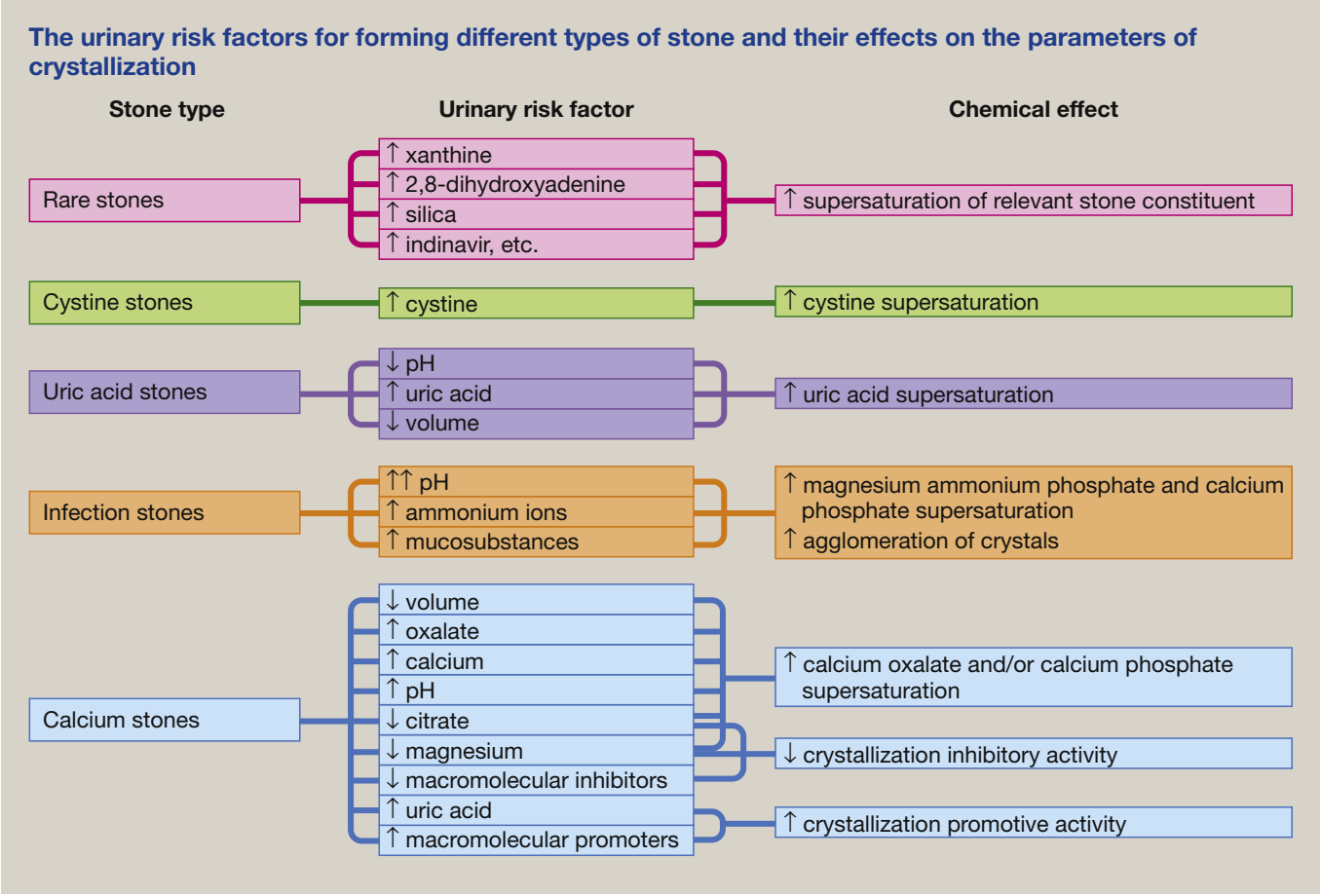

Figure 1

pain, plus visible or non-visible haematuria and graveluria. Classical renal or ureteric colic pain rises to a crescendo, causing the patient to writhe around, unable to find a comfortable position. The pain can radiate to the groin and genital region, depending on the location of a stone, and be accompanied by nausea and vomiting.

Normal range of urinary excretion of important stone constituents and stone risk factors

Urinary constituent	Normal 24-hour excretion (mmol)
Calcium	2.5–8 (men) 2.0–6.0 (women)
Oxalate	0.15–0.45 (1.0–3.0 in primary hyperoxaluria)
Uric acid	2.0–5.5 (men) 1.5–5 (women)
Citrate	0.5–5 (men) 1.0–5.0 (women) (<0.5 in distal renal tubular acidosis)
Cystine	<0.01 (0.5–3.0 in cystinuria)

Table 1

A patient with colic from an obstructing stone typically presents with a sudden onset of acute loin pain, often at night when the urine is maximally concentrated.

Investigations

Urinalysis

Urine analysis by dipstick in a patient with renal colic from a stone usually shows the presence of blood and protein, and can be positive for leucocytes, even in the absence of infection. However, in up to 15% of patients, dipstick tests are negative and these cannot exclude a stone. Stone-forming crystals can sometimes be seen in the urine on microscopy.

An associated urinary tract infection should always be considered, especially if urine dipstick testing is nitrite-positive, and a midstream urine sample should be sent for culture. Infection in the presence of an obstructing stone is potentially serious; it must be treated promptly with antibiotics, and the patient referred for urological management.

Imaging

Kidney–ureter–bladder (KUB) X-ray: urinary calculi that are rich in calcium are radio-opaque. Stones containing calcium phosphate are usually the most radio-opaque, with a density similar to bone. Magnesium ammonium phosphate (struvite) stones are less radio-opaque than calcium phosphate stones.

Radiolucent stones include pure cystine or uric acid, xanthine, dihydroxyadenine, indinavir, triamterene and matrix (infection). These stones are often missed on a plain abdominal (KUB) X-ray, but are easily seen (as radio-opaque) on a non-contrast CT scan (with the exception of indinavir and related protease inhibitor stones, and some matrix stones, which, owing to their gelatinous nature and relative lack of calcium, remain radiolucent).

Ultrasound scanning: this is a useful non-invasive method of detecting kidney stones, but it is operator-dependent and can overdiagnose renal stones. Ultrasound also has a high false-negative rate for identification of ureteric stones, which restricts its utility in an acute episode (see CT-KUB, below). It can detect the presence of hydronephrosis, and colour Doppler scanning can demonstrate an increase in resistive index in an obstructed kidney, as well as asymmetry or absence of ureteric (expulsed urine) 'jets'; however, these features do not always reliably diagnose obstruction, which can require an intravenous urogram or dynamic (radionuclide) renogram scan. Ultrasound scanning is a useful screening method when following patients with a history of recurrent stones, and avoids the need for multiple CT scans and the potential cumulative radiation risk. In a randomized trial, the diagnostic accuracy of ultrasonography was similar to that of a CT scan in diagnosing patients with suspected stones in an acute setting.[4]

Intravenous urography (IVU): the administration of intravenous contrast media is still a useful investigation in diagnosing an obstructing urinary tract stone. The sensitivity of IVU in detecting ureteric stones is 92%. IVU is still currently the first choice in diagnosing medullary sponge kidney, an often difficult but important diagnosis to make. However, CT urography seems to have similar diagnostic accuracy in this setting.

Computed tomography (CT-KUB): an unenhanced (non-contrast) CT scan is now the gold standard investigation in most hospitals in the diagnosis of urinary tract stones in an emergency. CT-KUB is reported to have a sensitivity of 97% and a specificity of 96%. Scans can be done rapidly and do not require contrast, and they are cost-effective when compared with IVU. Another advantage is that a CT scan can detect non-urological abnormalities relevant to the differential diagnosis of urinary tract stones, such as a ruptured ovarian cyst or acute appendicitis. However, a potential disadvantage is the higher dose of radiation exposure compared with current IVU. The only stones that can be 'invisible' on CT scanning are protease inhibitor (e.g. indinavir) stones in patients taking antiretroviral treatment; however, these are usually visible using ultrasound.

Treatment during the acute episode

Most patients with renal colic require prompt therapy for pain. A non-steroidal anti-inflammatory drug (NSAID), such as diclofenac, given intramuscularly or as a 100 mg suppository that is rapidly absorbed, is safe and effective. Opioids such as pethidine can be used, but can worsen the symptoms of nausea and vomiting caused by renal colic, with a small risk of addiction in patients with recurrent renal stones. NSAIDs also reduce renal blood flow, lowering urine output and intrapelvic pressure, but can aggravate pre-existing renal impairment, especially if the patient is elderly and has become volume-depleted after prolonged nausea and vomiting.

Concomitant use of an α-adrenoceptor blocker such as doxazosin (400 micrograms orally daily for 7–10 days), or a calcium antagonist such as nifedipine (as a single oral dose of 10–20 mg), to relax the ureter can improve the likelihood that a distal ureteric stone will be passed spontaneously.

Lists of analyses carried out as part of a stone screen procedure

Sample	Analyses performed
Stone	Quantitative infrared analysis for mineral constituents
Blood	Urea, creatinine, sodium, potassium, bicarbonate, albumin, calcium, magnesium, phosphate, urate, alkaline phosphatase, parathyroid hormone and 25(OH)-vitamin D, oxalate (in cases of severe hyperoxaluria)
Spot urine	Creatinine, urea, pH, calcium, phosphate, oxalate, urate, sodium, potassium, magnesium
24-hour urine measurements	Volume, pH, creatinine, calcium, magnesium, phosphate, oxalate, citrate, urate, urea, sodium, potassium, protein
	Qualitative cystine; if this is positive, quantitative cystine, ornithine, arginine and lysine
Diet diary	Fluids, water, calories, calcium, magnesium, phosphate, oxalate, total protein, animal protein, meat + fish + poultry protein, fruit + vegetable + cereal protein, dairy protein, purine, fat, refined carbohydrates, fibre, sodium and potassium

Table 2

Metabolic screening

After resolution of the acute stone episode, patients with a previous or family history of stones, or who are thought to be at higher risk, for example because of diabetes mellitus or hypertension, should undergo a complete 'metabolic' stone screen. Ideally, they should be studied on their normal and 'free' home diet at least 1 month after any procedure for removing a stone (as patients who have recently experienced a symptomatic renal stone-related episode are much more likely to stick to any dietary advice they have been given).

A comprehensive stone screen should include analysis of blood and spot urine samples (taken fasting, if possible), and two 24-hour urine collections (usually made on consecutive days), analysed as in Table 2. During the week before the 24-hour urine

Medical methods of preventing of urinary stones

Stone type	Treatment
2,8-Dihydroxyadenine	High fluid intake (>3 litres/day) + allopurinol (300 mg/day)
Silica	Discontinue magnesium trisilicate antacids
Xanthine	Hereditary form: high fluid intake + oral alkali (urine pH >7.4) Iatrogenic form: withdraw allopurinol
Cystine	High fluid intake (>3 litres/day) + oral alkali (urine pH >7.5), or D-penicillamine or α-mercaptopropionylglycine or tiopronin
Uric acid	High fluid intake (>2.5 litres/day) + oral alkali (urine pH >6.2), reduce purine intake
Infected	High fluid intake + antibiotics + cranberry juice (to ↓ pH <6.2)
Calcium	
Idiopathic	High fluid intake + relevant dietary advice and thiazide diuretic: bendroflumethiazide (5 mg) or chlortalidone (25 mg); or potassium citrate (1–2 × 30 mEq/day)
Hyperparathyroid	Parathyroidectomy or, if contraindicated, high fluids + dietary advice
Familial hyperoxaluria	High fluid intake (>3 litres/day) + pyridoxine (300 mg)
Enteric hyperoxaluria	High fluid intake + low-oxalate/high-calcium diet or potassium citrate
Distal renal tubular acidosis	High fluid intake + alkali (1–2 mEq/kg per day potassium citrate or sodium bicarbonate)
Medullary sponge kidney	Treat as for idiopathic (secondary distal renal tubular acidosis may be present)
Corticosteroid-induced	Discontinue corticosteroids; treat as for idiopathic
Sarcoidosis	High fluid intake and corticosteroid therapy if needed
Milk-alkali syndrome	Stop alkali, limit calcium, increase fluids
Vitamin D intoxication	Stop high vitamin D intake + increase fluids
Immobilization	Increase fluids; mobilize and treat any urinary tract infection with antibiotics; bisphosphonates or thiazides, if immobilization is prolonged
Iatrogenic	Discontinue drug concerned and replace with alternative therapy + high fluid intake

Table 3

collections, the patient should (ideally) complete a 7-day diet diary. Patients and medical staff are encouraged to send all stone material for quantitative spectrophotometric analysis.

Surgical management

Current practice is for patients with asymptomatic stones to be offered treatment; left untreated, >70% of these stones are likely to increase in size, dislodge and cause symptoms.[3] Extracorporeal shock-wave lithotripsy (ESWL) can be recommended for stones <20 mm in size; contraindications are pregnancy and concurrent anticoagulation. Success rates for ESWL vary from 30% to 100%. Treating large stones with ESWL risks producing multiple stone fragments impacted in a ureter (*Steinstrasse*), which can cause kidney obstruction unless a ureteric stent is in place. It can take several weeks to know if ESWL has been successful. Renal stones that do not respond to ESWL can be treated by flexible ureterorenoscopy if they are not too large (<20 mm). Stones that are 20 mm or larger, and those in a calyceal diverticulum or lower pole calyx, are better treated by percutaneous nephrolithotomy.

Medical management of recurrent kidney stones (Table 3)

The mainstay of prevention of kidney stone recurrence is represented by increased water intake, which, together with diet and lifestyle changes, represents the first line of treatment. The DASH (Dietary Approach to Stop Hypertension) diet, also known as the Mediterranean diet, which emphasizes a higher proportion of fruit and vegetables, low-fat dairy products and whole grains, and contains only small amounts of meat, sweets and sugar-containing beverages, has been associated with a lower risk of kidney stones and also has other health advantages. In patients with recurrent or active disease, thiazides (to reduce calcium excretion in patients who are hypercalciuric), potassium citrate (to boost citrate excretion, increase urine pH in uric acid and cystine stones, and offset potassium losses from diuretic use) or allopurinol can be tried.[5] ◆

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