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Urolithiasis and its Management

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Abstract

Urolithiasis is a disease known from ancient times, but still now the causes responsible for the formation of some of the different kind of stones are unknown, and consequently efficient therapeutic treatments have not yet been developed. Renal tract stones are common, more so in men, and among Asians and Caucasians, especially in warm climates. They are associated with a greater consumption of animal protein and refined foods, and decreased fluid intake. There are several types, most commonly consisting of calcium phosphates and oxalates; others are composed of magnesium ammonium phosphate (struvite), uric acid or cystine. Struvite stones are associated with urinary tract infections, often of urease-secreting bacteria that increase urinary ammonium concentration. Calcium stones may form for a number of reasons, including hypercalciuria and hyperoxaluria. Hypercalciuria may arise from changes to calcium resorption from bone, or renal and gastrointestinal tract handling of calcium; these are often associated with changes to parathyroid hormone secretion. Hyperoxaluria can arise from increased production or increased gut absorption. Other factors causing hypercalciuria include renal tubular acidosis or conditions that reduce the urinary concentrations of certain inhibitors, such as citrate and magnesium. Uric acid and cystine stones can form as a result of increased production or urinary concentration of the primary constituents. The assessment, investigation and management of patients with different types of stones are described.
Key words: Renal stone disease, Ureteric colic, Urolithiasis, Stone aetiology.

Introduction

Urolithiasis denotes stones originating anywhere in the urinary tract, including the kidneys and bladder. However, the pathophysiologic bases for the formation of kidney and bladder stones are

entirely different. Kidney stones form as a result of physicochemical or genetic derangements leading to supersaturation of the urine with stone-forming salts or, less commonly, from recurrent urinary tract infection with urease producing bacteria. Stasis in the upper urinary tract due to local anatomic anomalies may also promote or enhance stone formation in susceptible individuals. In contrast, bladder stones form almost exclusively as a result of urinary stasis and/or recurrent infection due to bladder outlet obstruction or neurogenic bladder. [1-4]

I. Clinical features

1) Pain is the most common presenting symptom of ureteric calculi and is caused by the stone obstructing the urinary tract. The three most common sites of obstruction are the pelviureteric junction, pelvic brim and vesicoureteric junction (although obstruction can occur at any point along the system).

Classical renal colic is characterized by an acute onset of pain in the loin that radiates to the groin and scrotum (or labia majora). Often, the pain is severe and the patient will move around to obtain relief. Unlike conditions causing peritonism, the pain is not relieved by remaining motionless. Nausea and vomiting are also common with acute renal colic, in part due to a degree of ileus.

Non-obstructing calculi may present with loin and/or groin pain, but pain which is less severe than that due to stones causing obstruction. Stones within the bladder will usually cause lower urinary tract symptoms such as dysuria, suprapubic discomfort, urgency and an unsuccessful desire to void.

2) Haematuria is present in 85–90 % of patients with stone and is usually microscopic (although frank blood may be observed). Haematuria may be absent (even on dipstick analysis) in up to 15% of patients.

3) Infection may be a causal factor in stone formation or may be secondary to obstruction caused by the calculus. Typically, infection with urease-producing organisms causes alkalinization of the urine, leading to formation of magnesium ammonium phosphate stones which may become large staghorn calculi. Any obstructing calculi can lead to secondary infection in the system proximal to the level of blockage. Severe infection can lead to frank pus in an obstructed system (pyonephrosis). The clinical presentation of the infected system can vary from asymptomatic bacteriuria to fulminant urosepsis. The condition will lead to renal damage and possibly death if untreated. [1-3]

II. Epidemiology

A. Intrinsic factors

1) **Age and sex:** peak incidence is between age 20 and 40 years. The male to female ratio is 3:1 and this is due in part to lower testosterone levels providing protection for women and children against developing oxalate stones, as testosterone may increase hepatic oxalate production.

2) Genetics: 25% of patients with kidney stones have a family history; in a study of 38,000 male health professionals, a family history of stones was more than three times more common in men with kidney stones than in non-stone-formers. Renal stones are rare in black Americans, black Africans, native Americans and Australian aborigines, but more common in Asians and Caucasians. Familial renal tubular acidosis, cystinuria and xanthinuria are hereditary disorders that lead to stone formation.

B. Extrinsic factors

1) Geography: high-incidence areas include the USA, the British Isles, Scandinavian countries, Mediterranean countries and central Europe. Low-incidence areas include Central and South America, and Africa. [3]

2) Climate and season: renal stones are common in hot climates and the incidence is increased after peak temperatures during the hot summer months. Increased sweating leads to concentrated urine and urinary crystal formation. A further problem for patients who develop uric acid and cystine calculi is that concentrated urine is more acidic, which encourages these stones to precipitate. Increased vitamin D production during summer, from increased exposure to sunlight, may lead to increased stone formation as a result of raised urinary calcium excretion.

3) Diet: increased incidence of renal calculi is associated with a more 'affluent' diet (increased animal protein, refined sugar and salt). Animal protein increases urinary calcium, oxalate and uric acid and, along with causing more acidic urine, contributes to calcium oxalate over-saturation and precipitation. A lower prevalence of stone disease is present in vegetarians in the UK. Interestingly, a higher dietary calcium intake (e.g. two glasses of milk per day) is strongly associated with a decreased risk of kidney stones. However, dietary calcium supplementation is not protective. Sucrose increases urinary calcium and oxalate concentrations. A lack of dietary fiber is also thought to contribute to stone formation, because fiber traps and decreases the rate and extent of absorption of sucrose and animal protein.

4) Water intake: increased water intake leads to urinary dilution of the constituents that may precipitate, as well as reducing the average time of residence of free crystal particles in urine. A low fluid intake (<1200 ml/day) predisposes to stone formation.

5) Occupation and stress: sedentary occupations, including professional and managerial groups, are associated with a higher incidence of urinary calculi than manual jobs. Stress is also associated with stone disease. [3, 4]

III. Physical chemistry

1) Supersaturation

When a substance is dissolved in water, the solution is 'saturated' when the concentration is high but crystals have not formed. As the concentration is increased further, crystals precipitate. The point at which saturation is reached and crystallization begins is the 'thermodynamic solubility product' (Ksp). This is a constant under specified conditions of temperature and pH, as changes to either will alter the amount of crystallization. It is important to be aware of crystallization

studies performed at room temperature rather than at body temperature. Urine is a more complex solution, and crystallization does not occur in urine when the solubility product in water is reached. This is because urine has the capacity to hold more solute than water as it contains a mixture of many electrically active ions that interact with each other, affecting their solubility. The presence of organic molecules, such as urea, uric acid and citrate, affects the solubility of other substances. Urine is therefore described as being 'metastable'. As the concentration of the substance is increased further, a point is reached when it eventually crystallizes and this concentration is known as the 'formation product' (KF) of the substance. Therefore, the metastable range can be described as the range between the Ksp and the KF. [4, 5]

2) Crystal formation

There are three processes of crystallization: nucleation (formation of crystals), crystal growth and agglomeration (crystals aggregate together to form larger particles). Two types of nucleation exist: 'homogeneous nucleation', which is the formation of the earliest crystal that will not dissolve, and 'heterogeneous nucleation', which is the formation of crystals on surfaces (e.g. cells, debris, urinary casts and other crystals). There are two theories behind crystal formation (Figure 1).

- The 'free-particle' theory describes the spontaneous precipitation of crystals in supersaturated urine. Crystals grow/aggregate sufficiently during the transit time of urine in the kidney. One of the newly formed nuclei grows enough such that that it is trapped at a narrow point in the renal tract to form a nidus for stone formation.
- The 'fixed-particle' theory claims that nuclei cannot grow sufficiently during the transit time of urine in the kidney but, if a crystal forms, it adheres to the renal epithelium, possibly because of increased stickiness of the epithelium or damage to the cell walls (caused by crystals or by viruses and bacteria).

Modifiers of crystal formation

Substances that alter or modify crystal formation exist in urine. They have been described with respect to calcium-containing stones, but not struvite (magnesium ammonium phosphate), cystine or uric acid stones. [4, 5, 6]

- Inhibitors slow or inhibit the rate of growth/aggregation of crystals or reduce adherence of crystals to the renal epithelium. Examples include magnesium, citrate, pyrophosphate and urinary glycoproteins, such as nephrocalcin and non-polymerized Tamm–Horsfall protein (or uromodulin).
- Promoters stimulate crystallization; examples include matrix substance A and other urinary glycoproteins, such as uromucoid, the polymerized form of Tamm–Horsfall protein.

3) Crystalluria

This is the production of crystals in urine and is an important requirement for stone formation. It occurs more frequently in urine from stone-formers. The crystal size within the urine is associated with the severity of the disorder, as defined by the stone episode rate.

4) Stone matrix

Renal stones also contain matrix, a non-crystalline material. The matrix content of a stone may be between 10 and 65% by weight, and tends to be higher when there is an associated urinary tract infection. It has been suggested that alteration in the secretion of renal enzymes (decreased urokinase and increased sialidase) may increase matrix formation. Certain bacteria, such as *Proteus mirabilis* and *Escherichia coli*, alter urokinase/sialidase activity leading to matrix formation, in turn causing increased crystal adherence to the renal epithelium. [5, 6, 7]

IV. Idiopathic stone formation

This is the commonest problem and supersaturation of the urine with calcium is a prerequisite for calcium stones to form; stone formation is impossible if urine is undersaturated. Between 30 and 60% of patients have increased urinary calcium excretion in the absence of raised serum calcium levels, defined as idiopathic hypercalciuria. Hypercalciuria contributes to stone formation by increasing the relative supersaturation of urine. Three types have been described.

- In absorptive hypercalciuria the main abnormality is increased intestinal calcium absorption. Serum calcium is normal and parathyroid hormone (PTH) secretion is suppressed.
- Renal hypercalciuria is due to leakage of calcium from the kidneys. Serum calcium is normal but PTH secretion is stimulated, thus distinguishing renal from absorptive hypercalciuria.
- Resorptive hypercalciuria is due to excessive bone resorption of calcium, as a result of increased PTH.

A. Metabolic causes of stone formation

1). Hypercalcaemia: almost all patients with hypercalcaemia who form stones have primary hyperparathyroidism. PTH increases osteoclast activity, calcium reabsorption and vitamin D3 production in the kidney. The PTH level is raised in more than 90% of patients, with a solitary adenoma of the gland being the cause in 80% of cases. The mainstay of treatment is surgical removal of the adenoma, with 90–100% improvement in stone recurrences. Other causes include sarcoidosis, hyperthyroidism and vitamin D toxicity. [8, 9]

2). Hyperoxaluria is another cause of calcium stone formation and there are two types.

- Primary hyperoxaluria is a rare genetic disorder causing increased hepatic oxalate production. Pyridoxine decreases oxalate production in some patients.
- In enteric hyperoxaluria, malabsorption (including small bowel resection) increases exposure of the colon to bile salts, which causes increased permeability of the colon to oxalate. A combination of oral hydration and a low-oxalate low-fat diet may be used. Oral calcium carbonate binds oxalate in the gut so that it cannot be absorbed. Cholestyramine, which binds fatty acids, bile salts and oxalate, may be used but is poorly tolerated.

3). RTA results from a defect of renal tubular H+ secretion, which decreases the ability of the kidney to acidify urine. The alkaline urine increases urinary calcium phosphate supersaturation,

leading to calcium phosphate stones. Treatment is directed at correcting systemic acidosis, with alkali therapy and raising urinary citrate. [10]

4). Hyperuricosuria is seen in 10–40% of calcium stone-formers. Hyperuricosuria promotes calcium oxalate crystallization. The main cause is excessive dietary purine intake. Purine restriction by limiting red meat, poultry and fish intake reduces hyperuricosuria.

5). Hypocitraturia is seen in 15–63% of patients with calcium stones. Citrate is not only a complexing agent for calcium, creating a more soluble complex than calcium oxalate, but it also inhibits calcium oxalate crystal formation and growth. The main cause of decreased citrate excretion in the urine is metabolic acidosis (RTA, inflammatory bowel disease and chronic diarrhoea, which results in intestinal alkali loss and metabolic acidosis).

6). Hypomagnesuria: there is a low urinary magnesium concentration in patients with stones, commonly associated with hypocitraturia. The main cause is malabsorption due to inflammatory bowel disease. [10]

Management

It is difficult to dissolve calcium stones, so an important aspect of patient management is preventing further formation once clearance has been achieved.

- Patients should be encouraged to drink plenty of clear fluids to maintain a urinary output of more than 2 litres/day.
- Diet should include limiting daily meat (protein) intake and increasing dietary fibre (e.g. natural fibre cereals, wholewheat rather than white bread), and limiting oxalate-rich foods, salt and excessive dairy products.
- Thiazides promote calcium resorption in the kidney.
- Orthophosphates decrease urinary calcium excretion.
- Sodium cellulose phosphate is a non-absorbable resin that binds calcium and decreases calcium absorption from the intestine, but must be used with caution.
- Potassium citrate may be used for treatment of hypocitraturia.
- Magnesium citrate, used to treat hypomagnesiuria, increases urinary magnesium and citrate.

B. Uric acid stones

Purines are metabolized to uric acid, which exists either as ionized urate salt (soluble) or undissociated uric acid (insoluble). The dissociation constant for uric acid is near 5.35; at this pH, half of the uric acid is present as the urate salt and the other half as free uric acid. As the pH decreases, more uric acid precipitates out of solution. Patients with uric acid stones or gout show increased production of uric acid, although the cause is unknown. Characteristically, patients have acidic urine, increased hyperuricosuria and reduced volumes of urine. Severe hyperuricosuria is also caused by myeloproliferativem disorders, such as leukaemia, owing to increased cell turnover. Cell necrosis occurs when patients are started on cytotoxic chemotherapy, which can lead to massive hyperuricosuria. To prevent this, patients should be started on allopurinol before chemotherapy. [10, 11, 12]

Management

It is important to assess the degree of purine ingestion and water intake. Investigations involve measuring urinary pH and uric acid, serum uric acid levels and examining the urine for uric acid crystals. Uric acid stones are radiolucent and can form large staghorn calculi. Medical therapy is successful in dissolving renal uric acid stones, and alkalinization and hydration dissolve near complete uric acid staghorn calculi. Treatments include:

- Oral hydration
- Urine alkalinization to pH 6.5–7.0
- Allopurinol, if the patient has hyperuricaemia or hyperuricosuria (>1200 mg/day), as it reduces production of uric acid from xanthine
- Diet.

C. Struvite stones

Struvite stones, composed of magnesium ammonium phosphate, are also known as 'infection stones', and account for 15–20% of all stones. Certain bacteria, such as *P. mirabilis* and *Ureaplasma urealyticum*, secrete the enzyme urease which hydrolyses urea to carbon dioxide and ammonium molecules. This reaction causes urinary pH to rise. As mentioned previously, *E.coli* decreases urokinase and increases sialidase activity, causing increased matrix production, thereby leading to crystal adherence to the renal epithelium. This explains how non-urease-producing bacteria may be associated with struvite stones. Struvite calculi account for the majority of staghorn stones. [11, 12]

Management

Patients may present acutely with loin pain, haematuria, fever, dysuria and frequency. Alternatively a large number of patients may present with malaise, weakness and loss of appetite. Struvite stones are usually radio-opaque on radiography. The main aim of treatment is first to remove the stone completely and then to provide medical therapy to prevent recurrent urinary tract infection:

- A combination of percutaneous nephrolithotomy (PCNL) and extracorporeal shock-wave lithotripsy (ESWL) is commonly used to clear stones
- Antibiotics sterilize the urine and prevent stone recurrence/ growth after operative procedures
- Acetohydroxamic acid is similar in structure to urea and a potent irreversible inhibitor of urease, although side effects limit its use.

D. Cystine stones

Cystine stones account for 1% of all stones, and occur only in patients with cystinuria. Cystinuria, an autosomal recessive disease causing decreased cystine resorption in the proximal tubule, affects 1 in 20,000 individuals; the peak age of incidence is 20–30 years. Cystine stones are often multiple, large, can form staghorn stones and are radio-opaque. [11, 12]

Management

Investigations include examining urine for cystine crystals, colorimetric testing and amino acid chromatography. The aim of treatment is to reduce the cystine concentration in urine by the following means:

- Low-methionine diet (cystine is a breakdown product of methionine, present in meat, fish and dairy products)
- Oral hydration
- Alkalinization of urine to a pH of more than 7.5, which allows dissolution of the stone
- Acetazolamide augments alkalinization, by inhibiting carbonic anhydrase, thereby increasing urinary bicarbonate excretion
- D-penicillamine or α-mercaptopropionylglycine, whichs bind cystine, making it soluble in urine
- Surgery to debulk/remove the stone.

V. Pathophysiology

CaOx stones are the most common stone type (60% of all stones), followed by the calcium phosphate subtypes hydroxyapatite (20%) and brushite (2%). Mixed calcium stones containing both calcium phosphate and CaOx are common. When over 30% of the stone volume is composed of calcium phosphate, it is classified as hydroxyapatite or apatite, depending on the crystal morphology. The basis for calcium stone formation is supersaturation of urine with stone-forming calcium salts. A number of dietary factors and metabolic abnormalities can change the composition or saturation of the urine so as to enhance stone-forming propensity. Among the metabolic conditions are hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, and gouty diathesis, and these conditions are reviewed in detail. Dietary factors also play a role in stone occurrence, and are discussed with regard to their role in preventing stone formation. [12]

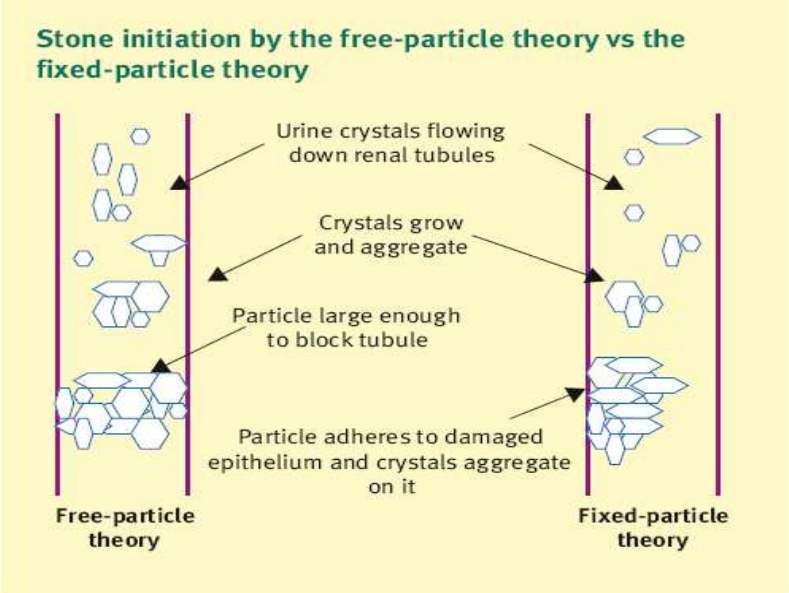

Figure1: Free particle theory Vs Fixed particle theory

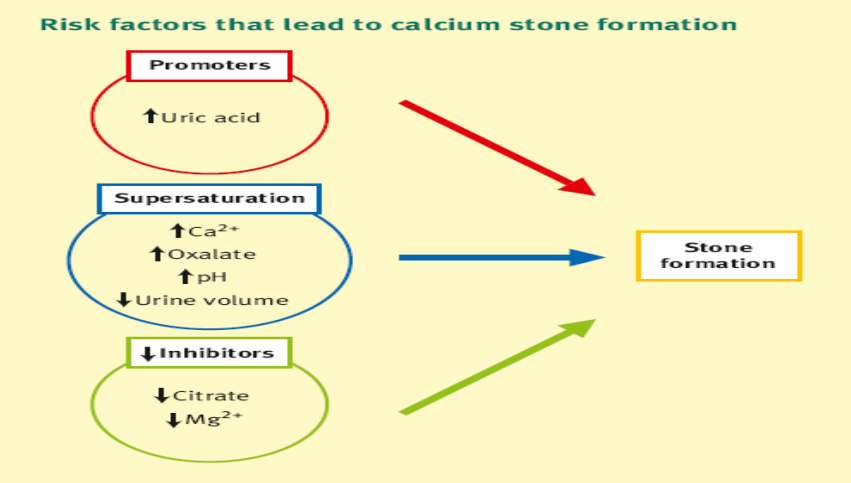

Figure 2: Risk factors that lead to calcium stone formation

Table 1: Causes and incidence of stones

Causes and incidence of stones

Disorder	Stone type	% of all stones
Idiopathic	Calcium oxalate/ phosphate	60–65
Hypercalcaemic states	Calcium oxalate/ phosphate	5–7
Hyperparathyroidism		
Sarcoidosis		
Hyperthyroidism		
Hyperoxaluric states	Calcium oxalate	1
Primary – enzyme deficiency		
Secondary – enteric hyperoxaluria		
Uric acid lithiasis	Uric acid	8
Gout		
Myeloproliferative disorders		
Renal tubular acidosis	Calcium phosphate	4
Cystinuria	Cystine	1–3
Xanthinuria	Xanthine	0.0001
Urinary tract infections	Magnesium ammonium phosphate	15–20

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