Pathophysiology of Stone Formation

Urinary tract stone formation is a complex event. The urine must be supersaturated (concentration above solubility product) with the stone-forming substances, such as calcium, oxalate, and uric acid. This can result from altered metabolism and abnormal excretion in urine. A supersaturated solution with concentration below formation product is metastable, and when the concentration exceeds the formation product, the solution is unstable and crystals will form. Citrate, magnesium, and large molecules like nephrocalcin and Tamm-Horsfall glycoprotein are all potent inhibitors of crystal growth and aggregation. Deficiency of inhibitors will increase the chance of stone formation even when the urine is in the metastable range.

Calcium stones may originate from subepithelial plaques composed of calcium phosphate crystals. They are first precipitated in the basement membrane of the thin loop of Henle and then accumulated in the subepithelial space of the renal papilla, forming the Randall plaques. The Randall plaques eventually erode through the papillary urothelium and constitute a stable anchoring surface for the growth of calcium oxalate stones. The non-crystalline components of stone account for about 2.5% of the stone by weight and are composed of a combination of mucoproteins, proteins, carbohydrates and urinary inhibitors.

Classification of Urinary Tract Stones

Urinary tract stones can be broadly divided into calcium and non-calcium ones. Up to 75% of all urinary tract stones are calcium stones. Both uric acid and infection stones occur in approximately 10% of the time, whereas cystine stones are rare (1%). Stones associated with medications and their by-products such as triamterene, adenosine, silica, indinavir and ephedrine are very uncommon and usually preventable.

Metabolic Evaluation

There have been lots of debates on the extent of metabolic evaluation required for patients with renal stones. An extensive metabolic evaluation may not be economically sound if it is applied to all first-time stone formers, unless the initial assessment puts them in a high-risk category for stone recurrence. The initial assessment should include a thorough medical history, including dietary and drinking habits. Patients should be screened for medical diseases that predispose them to stone diseases such as chronic bowel disease and gouty diathesis.

Baseline serum levels for blood urea, creatinine, calcium, phosphate, bicarbonate, and uric acid are checked. Urine microscopy for crystals, urine culture and pH are obtained. KUB may provide clues to the type of urinary tract stones. IVU or CT urogram is used to identify radiolucent stones and rule out anatomical abnormalities. Stone analysis is not always feasible or available, but this provides helpful information that can direct metabolic investigations and obviate the need for a more complex metabolic evaluation. For example, pure and mixed uric acid stones are strongly associated with a gouty diathesis and calcium phosphate dihydrate stones are associated with renal tubular acidosis. A more extensive metabolic evaluation, including 24-hour urine collection for volume, creatinine, calcium, oxalate and citrate, should be performed in patients with recurrent stone formation or
at increased risk for further stone formation (Figure 2) in order to identify the specific causes of stone disease and to direct a more specific medical treatment for these patients to prevent stone recurrence.

**Figure 2 Indications for a metabolic stones evaluation.**

### Medical Treatment

There are short-term emergency medical management for renal colic and stone dissolution therapy, and long-term pharmacological treatment to prevent stone recurrence.

#### Renal Colic

The cornerstone of renal colic management is analgesia, which can be achieved most expediently with parenteral narcotics such as morphine or non-steroidal anti-inflammatory drugs (NSAIDs). Anti-emetic agents such as metoclopramide and prochlorperazine may also be added. There is growing evidence that medical expulsion therapy (MET) can be efficacious especially for distal ureteric stones. Many randomised trials have confirmed the efficacy of MET in reducing the pain of stone passage, increasing the frequency of stone passage, and reducing the need for surgery. Tamsulosin (0.4mg daily), an α-1 selective adrenergic blocker that can relax the musculature of the distal ureter and lower urinary tract, has been the most commonly α-adrenergic blocker studied. Some other studies have also demonstrated that Terazosin (4mg daily) and Doxazosin (4mg daily) are equally effective. In addition, calcium channel blockers like Nifedipine have also been shown to enhance stone passage. Overall, MET is associated with a 65% greater likelihood of stone passage.

#### Stone Dissolution

Stone dissolution therapy is possible only with non-calcium stones. Uric acid and cystine stones can be dissolved by alkalinisation of the urine. Patients with uric acid stones can be treated with a combination of oral alkalinising agent, allopurinol and a high fluid intake. An oral alkalinising agent with potassium bicarbonate or potassium citrate is the preferred agent because sodium bicarbonate can lead to high sodium load. The dose should be adjusted to maintain an urinary pH between 6.5 and 7.0 to avoid the potential deposition at higher alkalinity of calcium phosphate around the uric acid stones, which would make them undissolvable. On the other hand, cystine will require for dissolution a pH of over 8, a target not achievable by oral alkali intake. Intrarenal alkalinisation may be performed under a low pressure system through a percutaneous nephrostomy tube or a retrograde catheter. Agents such as sodium bicarbonate and tromethamine (organic amine proton acceptor used as emulsifier in eye drops, not available in Hong Kong as pure agent) can be instilled directly to dissolve both uric acid and cystine stones. Likewise, after surgical removal of infective stones, residual fragments may be dissolved by urine acidification with hemiacidrin (a mixture of citric acid, gluconolactone and magnesium carbonate, not available in Hong Kong) irrigation. This agent should be employed only after urinary tract infection or colonisation has been brought under control, and careful monitoring of serum magnesium level is required.

### Stone Prevention

Over the past two decades, there has been dramatic advance in the minimally invasive and noninvasive managements of urinary tract stones. However, these surgical treatments can only remove the stones but cannot alter the course of the disease. First-time stone formers have often been estimated to have a 50% risk of recurrence within the subsequent 10 years. Long-term pharmacological treatment plays an important role to prevent stone recurrence. It is generally agreed that patients with uric acid, cystine and infection stones should always be treated pharmacologically. However, the cause of calcium stone disease is so variable that specific medical therapy should be reserved for high-risk patients.

#### Calcium Stones

General advice about dietary and drinking habits should be reinforced for all patients regardless of the underlying cause of the calcium stone disease. The general recommendation is to maintain a high urine flow by a generous intake of fluids. The aim should be to obtain a 24-hour urine volume of at least 2 litres. Citrus juices like lemon and orange juices have long been used as an adjunct to water to provide an increased urine volume as well as increased urinary citrate excretion. Excessive consumption of animal protein increases urinary calcium, oxalate and uric acid excretion, and it is recommended that animal protein intake be limited to 0.8 to 1.0g/kg body weight per day. The daily sodium intake should not exceed 3 gm because a high consumption of sodium will increase calcium excretion by reducing tubular reabsorption. Urinary citrate is also reduced due to loss of bicarbonate and the risk of forming sodium urate crystals is also increased. Calcium intake should not be restricted as restriction probably leads to an increase in available intestinal oxalate and may subsequently increase oxalate absorption and hence calcium oxalate stone formation. The general recommendation of daily calcium requirement is 1000mg/day. Calcium supplements are not recommended except in cases of enteric hyperoxaluria, when additional calcium should be ingested with meals to bind intestinal oxalate. An excessive intake of oxalate-rich products should be limited or avoided to prevent an oxalate load. Spinach, cocoa and nuts are rich in oxalate. The intake of food particularly rich in urate should be restricted in patients with hyperuricosuric calcium oxalate stone disease, as
well as in patients with uric acid stone disease. The intake of urate should not exceed 500mg/day. Examples of food rich in urate include liver, kidney and sardine. It is anticipated that with these fluid and dietary measures alone, a significant number of patients may be able to normalise their urinary risk factors for stone formation. After 3 to 4 months of conservative management, patients should be re-evaluated for persistence of metabolic abnormalities. If the patient's metabolic or environmental abnormalities have been corrected, the conservative management can be continued and the patient should be followed regularly to monitor the efficacy of treatment and to encourage the patient's compliance. If, however, a metabolic defect persists, a more selective pharmacological therapy may be instituted.

The ideal pharmacological agent should halt the formation of calcium stones, be free of side effects and be easy to administer. These aspects are all of utmost importance in order to achieve a reasonably good compliance to the probable life-long therapy. The most commonly used pharmacological agents are thiazides, potassium citrate, and allopurinol.

**Thiazide**

has a pronounced and well-documented effect in reducing the excretion of calcium in hypercalciuric patients. The hypocalciuric action of thiazide is mediated by increased reabsorption of calcium in the proximal as well as in the distal parts of the nephron. Thiazide might also decrease the excretion of oxalate, possibly by a reduced intestinal absorption of calcium. Hydrochlorothiazide can be given 50mg once or 25mg twice daily. Long-term treatment with thiazide and insufficient substitution with potassium might lead to hypokalaemia and a concomitant hypocitraturia. In addition, the effect of thiazide in reducing urinary calcium is counteracted by a high sodium intake. Long-term use of thiazide is to some extent limited by its side effects such as hypotension, weakness and impotence.

**Alkaline citrate**

has been advised as the method of choice to increase the excretion of urinary citrate for patients with hypocitraturia. Citrate will form complexes with calcium. This chelation reduces the ion-activity products of both calcium oxalate and calcium phosphate. Citrate is also an inhibitor of growth and aggregation of these crystals. The alkali load also reduces the tubular reabsorption of citrate in the nephron. The simultaneous urinary alkalinisation and a high urine citrate excretion therefore favourably counteract urine crystallisation. Clinical studies indicated that potassium citrate (20 mEq twice or thrice daily) is effective in stone prevention. However, the compliance with alkaline citrate was shown to be no better than 50% due to its unpalatability, gastrointestinal upset and the high cost of the available commercial preparations.

Treatment with allopurinol to counteract the formation of calcium oxalate stones was introduced following the demonstration of a relationship between hyperuricosuria and calcium oxalate stone formation. Being a xanthine oxidase inhibitor, the synthesis of uric acid from hypoxantine is reduced. The effect of allopurinol on calcium oxalate stone formation may be mediated through the reduced salting-out effect, decreased risk of uric acid or urate crystals as promoters of calcium oxalate precipitation, and/or reduced excretion of oxalate. Therefore, allopurinol can be used for treating patients with hyperuricosuric calcium oxalate stone formation but it is not recommended for patients with other biochemical abnormalities. Allopurinol can be given 300mg daily with good tolerance, but severe side effects like Steven Johnson syndrome have been reported.

**Uric Acid Stones**

Uric acid stones form in urine highly supersaturated with uric acid. The most common urinary abnormality is a low urine pH, often occurring with a small urine volume. Patients should be advised to adequate fluid intake to maintain a 24-hour urine volume of approximately 2 to 2.5L. The intake of animal protein should not exceed 0.8g/kg/day. In addition, alakinisation of the urine is mandatory and should preferably be carried out with potassium citrate. The pH should be increased to a level of 6.5 to 7.0. There might be a risk of calcium phosphate stone formation if the pH is raised to higher levels. A reduced excretion of urate can be accomplished with allopurinol when the 24-hour urate excretion exceeds 4mmol.

**Cystine Stones**

There is no known inhibitor for cystine stones, and cystine stone formation is completely dependent on excessive urinary cystine excretion. The objective of medical treatment is to reduce the urine concentration of cystine to below its solubility limit of 200 to 300mg/L. This requires a high fluid intake to attempt to produce a 24-hour urine volume of at least 3 litres, in order to reduce the supersaturation of urine cystine. In addition, the fluid intake should be evenly distributed during the day. A diet low in methionine (precursor to cystine) theoretically might reduce the urinary excretion of cystine but most of the cystine is endogenous and patient's compliance is usually poor. Restricted intake of sodium is probably more effective in reducing urinary cystine. As discussed before, increased solubility of cystine by oral alkali is not really practical, though this is usually given. When the combined effects of a high diuresis and alkalinisation are not enough to prevent stone formation, complex formation by chelating agents is necessary. Thiol compounds, such as D-penicillamine and α-mercaptopropionylgycine (MPG), are most commonly used. The latter compound seems to be associated with fewer side effects than penicillamine. The recommended daily dosage is 10-15mg/kg or 750mg/day. The administration of thiols should always be accompanied by pyridoxine to avoid vitamin B6 deficiency. A third alternative is captopril.

**Infection Stones**

Infection stones compose of magnesium ammonium phosphate. These stones are caused by urease-producing micro-organisms. It is fundamental that the renal collecting system is cleared of stone materials to prevent recurrence. After complete surgical removal of the infection stones, recurrent infections with urea-splitting organisms should be prevented with improved bladder health, adequate urine drainage and suppressive antibiotics prophylaxis.
Conclusion

It is very important that the patient should be motivated to comply with the general measures of life-long interference with dietary and drinking habits. When combined with selective medical therapy in patients with high risks of stone recurrence, a remission rate of more than 80% and overall reduction in individual stone formation rate of more than 90% can be obtained. A satisfactory response should require continued, dedicated compliance of patients with the recommended programme and a commitment by the physician to provide long-term follow-up and care.

References

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