

# **Nephrolithiasis**

By Teshager Aklilu

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# Nephrolithiasis

- Nephrolithiasis, or kidney stone disease, is a common, painful, and costly condition.
- While a stone may form due to crystallization of lithogenic factors in the upper urinary tract, it can subsequently move into the ureter and cause renal colic.
- Pts who have had renal colic report that it is **the worst pain** they have ever experienced.

- There are various types of kidney stones.
- It is important to identify the stone type, which informs prognosis and selection of the optimal preventive regimen.
  - calcium oxalate stones are most common (~75%)
  - calcium phosphate (~15%)
  - uric acid (~8%)
  - struvite (~1%)
  - cystine (<1%) stones
- Many stones are a mixture of crystal types (e.g., calcium oxalate and calcium phosphate) and also contain protein in the stone matrix.
- Rarely, stones are composed of medications, such as acyclovir, indinavir, atazanavir and triamterene.

# Epidemiology

- Nephrolithiasis is a global disease.
- Data suggest an increasing prevalence, likely due to Westernization of lifestyle habits (e.g., dietary changes, increasing body mass index).
- $M > F$
- White > black
- Decreases as age increases

# Associated Medical Conditions

- Nephrolithiasis is a systemic disorder.
- Several conditions predispose to stone formation:
  - Gastrointestinal malabsorption (e.g., Crohn's disease, gastric bypass surgery)
  - Primary hyperparathyroidism
  - Obesity
  - T2DM
  - Distal renal tubular acidosis
- A number of other medical conditions are more likely to be present in individuals with a history of nephrolithiasis, including hypertension, gout, cholelithiasis, reduced bone mineral density, and chronic kidney disease

# Pathogenesis

- In the processes involved in crystal formation, it is helpful to view urine as a complex solution.
- A clinically useful concept is ***supersaturation*** (the point at which the concentration product exceeds the solubility product).
- However, even though the urine in most individuals is supersaturated with respect to one or more types of crystals, the presence of inhibitors of crystallization prevents the majority of the population from continuously forming stones.
- The most clinically important inhibitor of calcium-containing stones is urine **citrate**.

# Risk factors

- **Dietary Risk Factors**

- Dietary factors that are associated with an increased risk of nephrolithiasis include animal protein, oxalate, sodium, sucrose, and fructose.
- Dietary factors associated with a lower risk include calcium, potassium, and phytate.

- Higher dietary calcium intake is related to a *lower* risk of stone formation.
- The reduction in risk associated with higher calcium intake may be due to a reduction in intestinal absorption of dietary oxalate that results in lower urine oxalate.
- Low calcium intake is contraindicated as it increases the risk of stone formation and may contribute to lower bone density in stone formers



- Urinary oxalate is derived from both endogenous production and absorption of dietary oxalate.
- Owing to its low and often variable bioavailability, much of the oxalate in food may not be readily absorbed.
- However, absorption may be higher in stone formers.
- Dietary oxalate is only a weak risk factor for stone formation, urinary oxalate is a strong risk factor for calcium oxalate stone formation, and efforts to avoid high oxalate intake should thus be beneficial.

- Higher intake of animal protein may lead to increased excretion of calcium and uric acid as well as to decreased urinary excretion of citrate, all of which increase the risk of stone formation.
- Higher sodium and sucrose intake increases calcium excretion independent of calcium intake.
- Higher potassium intake decreases calcium excretion, and many potassium-rich foods increase urinary citrate excretion due to their alkali content.

- Vitamin C supplements are associated with an increased risk of calcium oxalate stone formation, possibly because of raised levels of oxalate in urine.
- Thus, calcium oxalate stone formers should be advised to avoid vitamin C supplements.

- The risk of stone formation increases as urine volume decreases.
- When the urine output is less than 1 L/d, the risk of stone formation more than doubles.
- Fluid intake is the main determinant of urine volume, and the importance of fluid intake in preventing stone formation.

- **Nondietary Risk Factors**

- Age, race, body size, and environment are important risk factors for nephrolithiasis.
- The incidence of stone disease is highest in middle-aged white men, but stones can form in infants as well as in the elderly.
- Weight gain increases the risk of stone formation
- Environmental and occupational influences that may lead to lower urine volume, such as working in a hot environment or lack of ready access to water are important considerations.

- **Urinary Risk Factors**

- lower urine volume results in increased concentrations of lithogenic factors and is a common and readily modifiable risk factor.

- ***Urine Calcium***

- Higher urine calcium excretion increases the likelihood of formation of calcium oxalate and calcium phosphate stones

- ***Urine Oxalate***

- Higher urine oxalate excretion increases the likelihood of calcium oxalate stone formation.
- The two sources of urine oxalate are endogenous generation and dietary intake.
- Dietary oxalate is the major contributor and also the source that can be modified.
- Higher dietary calcium intake reduces gastrointestinal oxalate absorption and thereby reduces urine oxalate.



- ***Urine Citrate***

- Urine citrate is a natural inhibitor of calcium-containing stones; thus, lower urine citrate excretion increases the risk of stone formation.
- Citrate reabsorption is influenced by the intracellular pH of proximal tubular cells.
- Metabolic acidosis will lead to a reduction in citrate excretion by increasing reabsorption of filtered citrate.

- ***Urine uric acid***

- Higher urine levels of uric acid—a risk factor for uric acid stone formation—are found in individuals with excess purine consumption and rare genetic conditions that lead to overproduction of uric acid.
- This characteristic does not appear to be associated with the risk of calcium oxalate stone formation.

- ***Urine pH***

- Urine pH influences the solubility of some crystal types.
- Uric acid stones form only when the urine pH is consistently  $\leq 5.5$  or lower, whereas calcium phosphate stones are more likely to form when the urine pH is  $\geq 6.5$  or higher.
- Cystine is more soluble at higher urine pH.
- Calcium oxalate stones are not influenced by urine pH.

- **Genetic Risk Factors**

- The risk of nephrolithiasis is more than twofold greater in individuals with a family history of stone disease.

- The two most common and well-characterized rare monogenic disorders that lead to stone formation are primary hyperoxaluria and cystinuria.
- **Primary hyperoxaluria** is an autosomal recessive disorder that causes excessive endogenous oxalate generation by the liver, with consequent calcium oxalate stone formation and crystal deposition in organs.
- Intraparenchymal calcium oxalate deposition in the kidney can eventually lead to renal failure.

- **Cystinuria** is an autosomal recessive disorder that causes abnormal reabsorption of filtered dibasic amino acids.
- The excessive urinary excretion of cystine, which is poorly soluble, leads to cystine stone formation.
- Cystine stones are visible on plain radiographs and often manifest as staghorn calculi or multiple bilateral stones.
- Repeat episodes of obstruction and instrumentation can cause chronic renal impairment.

# Recommendations

## 1. Calcium Oxalate

- Risk factors for calcium oxalate stones include higher urine calcium, higher urine oxalate, and lower urine citrate.
- This stone type is insensitive to pH in the physiologic range.
- Excessive calcium intake ( $>1200$  mg/d) should be avoided.
- A thiazide diuretic can substantially lower urine calcium excretion.
- Thiazide diuretics can reduce calcium oxalate stone recurrence by  $\sim 50\%$ .
- When a thiazide is prescribed, dietary sodium restriction is essential to obtain the desired reduction in urinary calcium excretion.

- A reduction in urine oxalate will in turn reduce the supersaturation of calcium oxalate.
- In pts with the common form of nephrolithiasis, avoiding high-dose vitamin C supplements is the only known strategy that reduces endogenous oxalate production.
- Oxalate is a metabolic end product; therefore, any dietary oxalate that is absorbed will be excreted in the urine.
- Reducing absorption of exogenous oxalate involves two approaches.
- First, the avoidance of foods that contain high amounts of oxalate, such as spinach, rhubarb, and potatoes, is prudent.



- Citrate is a natural inhibitor of calcium oxalate and calcium phosphate stones.
- Higher-level consumption of foods rich in alkali (i.e., fruits and vegetables) can increase urine citrate.
- For pts with lower urine citrate in whom dietary modification does not adequately increase urine citrate, the addition of supplemental alkali (typically potassium citrate) will lead to an increase in urinary citrate excretion.
- Sodium salts, such as sodium bicarbonate, while successful in raising urine citrate, are typically avoided due to the adverse effects of sodium on urine calcium excretion

- Restriction of nondairy animal protein (e.g., meat, chicken, seafood) is a reasonable approach and may result in higher excretion of citrate and lower excretion of calcium.
- In addition, reducing sodium intake to  $<2.5$  g/d may decrease urinary excretion of calcium.
- Sucrose and fructose intake should be minimized.

## 2. Calcium Phosphate

- Calcium phosphate stones share risk factors with calcium oxalate stones, including higher concentrations of urine calcium and lower concentrations of urine citrate.
- Higher urine phosphate levels and higher urine pH (typically  $\geq 6.5$ ) are associated with an increased likelihood of calcium phosphate stone formation.
- Calcium phosphate stones are more common in pts with distal renal tubular acidosis and primary hyperparathyroidism

- Thiazide diuretics (with sodium restriction) may be used to reduce urine calcium.
- In pts with low urine citrate levels, alkali supplements (e.g., potassium citrate) may be used to increase these concentrations.
- However, the urine pH of these pts should be monitored carefully because supplemental alkali can raise urine pH, thereby potentially increasing the risk of stone formation.
- Reduction of dietary phosphate may be beneficial by reducing urine phosphate excretion.

### **3. Uric Acid**

- The two main risk factors for uric acid stones are persistently low urine pH and higher uric acid excretion.
- Urine pH is the predominant influence on uric acid solubility; therefore, the mainstay of prevention of uric acid stone formation entails increasing urine pH.
- Alkalinizing the urine can be readily achieved by increasing the intake of foods rich in alkali (e.g., fruits and vegetables) and reducing the intake of foods that produce acid (e.g., animal flesh).
- If necessary, supplementation with bicarbonate or citrate salts (preferably potassium citrate) can be used to reach the recommended pH goal of 6 to 7 throughout the day and night.

- Urine uric acid excretion is determined by uric acid generation.
- Uric acid is the end product of purine metabolism; thus reduced consumption of purine-containing foods can lower urine uric acid excretion.
- The serum uric acid level is dependent on the fractional excretion of uric acid and therefore does not provide information on urine uric acid excretion.
- If alkalinization of the urine alone is not successful and if dietary modifications do not reduce urine uric acid sufficiently, then the use of a xanthine oxidase inhibitor, such as allopurinol or febuxostat, can reduce urine uric acid excretion by 40–50%.

#### **4. Cystine stone**

- Cystine excretion is not easily modified.
- Long-term dietary cystine restriction is not feasible and is unlikely to be successful; thus the focus for cystine stone prevention is on increasing cystine solubility.
- This goal may be achieved by treatment with medication that covalently binds to cystine (tiopronin and penicillamine) and a medication that raises urine pH.
- Tiopronin is the preferred choice due to its better adverse event profile.
- The preferred alkalinizing agent is potassium citrate as sodium salts may increase cystine excretion.
- As with all stone types, and especially in pts with cystinuria, maintaining a high urine volume is an essential component of the preventive regimen.

## 5. Struvite / Infection stone/ triple phosphate stone

- Struvite stones form only when the upper urinary tract is infected with urease-producing bacteria such as *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Providencia* species.
- Urease produced by these bacteria hydrolyzes urea and may elevate the urine pH to a supraphysiologic level (>8.0).
- Struvite stones may grow quickly and fill the renal pelvis (*staghorn calculi*).
- Struvite stones require complete removal by a urologist.
- New stone formation can be avoided by the prevention of UTIs.
- In pts with recurrent upper UTIs (e.g., individuals with surgically altered urinary drainage or spinal cord injury), the urease inhibitor **acetohydroxamic acid** can be considered; however, this agent should be used with caution because of potential side effects.



# Long term follow up

- In general, the preventive regimens described above do not cure the underlying pathophysiologic process.
- Thus these recommendations typically need to be followed for the pt's lifetime, and it is essential to tailor recommendations in a way that is acceptable to the pt.
- It is important to ensure that the preventive regimen has been implemented and has resulted in the desired reduction in the risk of new stone formation.