Urolithiasis – Epidemiology, Pathogenesis & Pathophysiology

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Epidemiology

• Lifetime prevalence of kidney stone – 1 – 15%
• Increasing incidence & prevalence worldwide
• Depends on
  • Age
  • Gender
  • Race
  • Geography / Climate
  • Occupation
  • BMI & weight
  • Water intake
Age

• Uncommon before age 20, peaks in 4\textsuperscript{th} – 6\textsuperscript{th} decades of life
Gender

• Affects men > women, 2-3X more in men

• Lower incidence in women have been attributed to the protective effect of estrogen against stone formation
  • Enhanced renal calcium absorption and reduced bone resorption (McKane et al, 1995; Nordin et al, 1999)
  • Heller and colleagues (2002) identified lower urinary saturation of calcium oxalate and brushite in women compared with men
Race

- Among the U.S. men, Soucie & colleagues (1994) - Highest prevalence in whites
- Whites → Hispanics → Asians → African-Americans
- Gender distribution of stone disease varies according to race
- Male:female for whites 2.3; 0.65 for African-Americans
Geography / Climate

• Higher prevalence in hot or dry climates like mountainous areas, tropical countries

• Highest incidence of stone disease in summer months
Occupation

- Heat exposure & dehydration – cooks, engineering room personnel, steel workers
BMI and weight

- Health Professionals Follow-Up study (600 stone forming men, 400 non-stone forming men), Nurses’ Health Study (900 stone forming, 400 non-stone forming older women) and Nurses’ Health Study II (700 stone formers, 300 non-stone formers) found that

- Subjects with higher BMI excreted more urinary oxalate, uric acid, sodium and phosphorus than those with lower BMI

- The association of obesity with calcium oxalate stone formation is primarily due to ↑ excretion of promoters of stone formation.
Water Intake

- Low volume intake – higher risk
- High volume intake – diluted urine, lower risk

(Curhan et al, 1993, 1997)
<table>
<thead>
<tr>
<th>Stone Composition</th>
<th>Occurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calcium-Containing Stones</td>
</tr>
<tr>
<td>Calcium oxalate</td>
<td>60</td>
</tr>
<tr>
<td>Hydroxyapatite</td>
<td>20</td>
</tr>
<tr>
<td>Brushite</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Non-Calcium-Containing Stones</td>
</tr>
<tr>
<td>Uric acid</td>
<td>7</td>
</tr>
<tr>
<td>Struvite</td>
<td>7</td>
</tr>
<tr>
<td>Cystine</td>
<td>1-3</td>
</tr>
<tr>
<td>Triamterene</td>
<td>&gt;1</td>
</tr>
<tr>
<td>Silica</td>
<td>&gt;1</td>
</tr>
<tr>
<td>2,8-Dihygroxyadenine</td>
<td>&gt;1</td>
</tr>
</tbody>
</table>

石成分组成及相对发生率

**Stone Composition and Relative Occurrence**
Stone formation

- Supersaturation of urine
- Concentration product at the point of saturation is called – thermodynamic solubility product, $K_{sp}$
- Below $K_{sp}$ $\rightarrow$ crystals won’t form. Above $K_{sp}$ $\rightarrow$ crystals should form but do not due to inhibitors.
- Formation product $K_{f}$
- Above $K_{f}$ $\rightarrow$ crystals would form despite the inhibitors
- The level between $K_{sp}$ and $K_{f}$ = metastable
- Undersaturated
- Metastable
- Unstable
Stone formation

• 3 processes
  • Nucleation
  • Crystal growth
  • Aggregation

• In normal human urine, concentration of calcium oxalate 4X more soluble than in water. Calcium oxalate precipitation only occurs when supersaturation exceeds solubility by 7 – 11 times.
Nucleation

• Homogeneous nucleation = nuclei form in pure solution
• Heterogeneous = involvement of foreign particles
• Heterogeneous nucleation – faster since foreign particles form the scaffold for the crystals to grow on
• In urine, crystal nuclei form through heterogeneous nucleation
2 THEORIES

<table>
<thead>
<tr>
<th>FIXED PARTICLE GROWTH THEORY</th>
<th>FREE CRYSTAL PARTICLE GROWTH THEORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxalate-induced injury (? Free radical formation) to renal tubular cells promotes adherence of calcium oxalate crystals → NUCLEATION</td>
<td>Initially thought free particle formation impossible within the normal transit time through the nephron (5 – 7 min)</td>
</tr>
<tr>
<td>Crystal growth → Aggregation → STONES</td>
<td>Recalculated with current nephron dimensions, supersaturation and crystal growth rates (Kok and Khan, 1994) → POSSIBLE</td>
</tr>
<tr>
<td></td>
<td>If sufficient nuclei form and grow, aggregation of the crystals → larger particles within minutes → occlude the tubular lumen</td>
</tr>
</tbody>
</table>
Vascular injury in pathogenesis of stones

• Stoller and colleagues (2004)

• Inciting event in the stone pathogenesis - vascular injury to the vasa recta near the renal papilla

• Repair of damaged vessels – atherosclerotic-like reaction → calcification of the endothelial wall → erosion into papillary interstitium and collecting ducts → nidus for stone formation
Stone Inhibitors

• Mainly for calcium oxalate and calcium phosphate
• No specific inhibitors for uric acid crystallization

• Citrate – the most important
• Magnesium
• Pyrophosphate
• Urinary glycoproteins – nephrocalcin, Tamm-Horsfall glycoprotein
Citrate as an inhibitor

- Complexes with calcium → reduces availability of calcium to interact with oxalate or phosphate
- Inhibits spontaneous precipitation of calcium oxalate
- Prevents agglomeration of calcium oxalate crystals
Tamm-Horsfall glycoprotein

- Expressed in thick ascending limb and distal tubule, and released into the urine
- Potent inhibitor of calcium oxalate aggregation
- Most abundant protein found in the urine
Mg as an inhibitor

• Mg complexes with oxalate $\rightarrow$ reduces oxalate concentration
• Also reduces the rate of calcium oxalate crystal growth
Inorganic pyrophosphate

- Responsible for 25 – 50% of the inhibitory activity of whole urine against calcium phosphate crystallization
Matrix

- Renal calculi – crystalline & non-crystalline components
- Matrix – non-crystalline component – heterogeneous mixture of proteins, carbohydrate, glycosaminoglycans etc.
- Percentage varies with stone types
- Higher (up to 65%) if associated with chronic UTI
- Exact role of matrix in stone formation, whether as a promoter, an inhibitor, or a passive bystander is unknown.
Calcium Metabolism

• Recommended daily calcium intake – 800 – 1200 mg/day

• Net absorption of calcium is about 200 mg/day

• Calcium is absorbed in the ionic state ➔ substances that complexes with calcium (phosphate, citrate, sulfate, oxalate, fatty acids) reduce the availability of ionic calcium for absorption

• Most important factor that mediates active or transcellular calcium absorption is 1,25-dihydroxyvitamin D3 or calcitriol
Calcium Metabolism

• Calcium in plasma in 3 forms:
  • Combined with plasma proteins (40%)
  • Combined with other substances but diffusible through capillaries (10%)
  • $\text{Ca}^{2+}$ (50%) active
Pathogenesis of renal stones

1) Hypercalciuria
2) Hyperoxaluria
3) Hypocitraturia
4) Hyperuricosuria
Hypercalciuria

• Common in stone-forming patients, occurring in 35 – 65% patients

• High urinary calcium ➔ increased saturation of calcium salts and reduce inhibitors activity by way of complexation

• Can be divided into 3 subtypes
  • Absorptive hypercalciuria
  • Renal hypercalciuria
  • Resorptive hypercalciuria
Absorptive hypercalciuria

- Increased urinary calcium excretion (>0.2mg/mg creatinine) after oral calcium load

- The abnormality is the intestinal HYPERabsorption of calcium → increased serum calcium → suppresses serum PTH → increase renal filtration of calcium → hypercalciuria

- The cause of increased intestinal absorption of calcium not fully understood
  - Upregulation of vitamin D receptor
  - Hypersensitivity to vitamin D
Renal hypercalciuria

The underlying abnormality is primary renal wasting of calcium.

The consequent reduction in circulating serum calcium stimulates PTH production.
Renal hypercalciuria

- High fasting urinary calcium levels (>0.11 mg/dL) with normal serum calcium are characteristic

- Actual cause of renal calcium leak → UNKNOWN
  - Renal injury, structural abnormalities, functional defects
Resorptive hypercalciuria

• Mostly associated with primary hyperparathyroidism – excessive PTH → excessive bone resorption, increased renal synthesis \( 1,25(OH)_2D_3 \)

• Rare causes
  • Hypercalcemia of malignancy
  • Sarcoidosis – production of \( 1,25(OH)_2D_3 \) from \( 1-\alpha \) hydroxylase in macrophages of the sarcoid granuloma
  • Thyrotoxicosis
  • Vitamin D toxicity
  • Glucocorticoid-induced hypercalcemia – promote bone resorption & reduce bone formation; stimulate PTH release; inhibit intestinal absorption
Idiopathic hypercalciuria

- Occurs in 5 – 10% of healthy people and in about 50% patients with calcium nephrolithiasis
Hyperoxaluria

- Defined as urinary oxalate >40 mg/day
- Leads to urinary saturation of calcium oxalate → calcium oxalate stones
- Implicated in renal tubular cell injury → fixation of calcium oxalate crystals and subsequent crystal growth

- Divided into
  - Primary hyperoxaluria
  - Enteric hyperoxaluria
  - Dietary hyperoxaluria
  - Idiopathic hyperoxaluria
Primary hyperoxaluria

• Rare autosomal recessive disorder

Figure 45-6. Pathway of oxalate metabolism in the liver. Defects in alanine:glyoxylate aminotransferase (AGT) are associated with primary hyperoxaluria type I (PH I), and defects in glyoxylate reductase/hydroxypyruvate reductase (GRHPR) are associated with primary hyperoxaluria type II (PH II). LDH, lactate dehydrogenase.
Enteric hyperoxaluria

• A/W malabsorption from any cause, including small bowel resection, jejunooileal bypass or chronic diarrhea conditions

Fat malabsorption → fatty acids binds calcium → reduce calcium pool for calcium oxalate formation → increase oxalate pool for reabsorption

• Fatty acids & bile salts also increase colonic permeability to oxalate

• Chronic diarrhea also cause dehydration, hypoK, hypoMg, hypocitraturia and low urine pH → all of which increase risk of calcium oxalate stone formation
Dietary hyperoxaluria

• Oxalate-rich foods – nuts, chocolate, brewed tea, spinach, broccoli, strawberries, rhubarb

• Overindulgence in such foods → hyperoxaluria

• Low calcium diet → more free oxalate for intestinal absorption → hyperoxaluria
Idiopathic hyperoxaluria

• Usually mild hyperoxaluria

• Several studies have suggested that mild hyperoxaluria is as important a factor as hypercalciuria in the pathogenesis of idiopathic calcium oxalate stones
  • Baggio and associates (1986) detected a higher rate of oxalate flux across the RBC membrane at steady state in 114 patients with a history of calcium oxalate kidney stones compared with control subjects
Hypocitraturia

• Exists in up to 10% calcium stone formers and a/w other abnormalities in 20 – 60% (Campbell)

• Defined as urinary citrate level < 320 mg/day or <0.6 mmol/day (men) or <1.03 mmol/day (women)

• Citrate
  • Complexes with calcium → reduces urinary calcium saturation
  • Prevents spontaneous nucleation of calcium oxalate
  • Inhibits growth of calcium oxalate & calcium phosphate crystals
  • Enhance inhibitory effect of Tamm-Horsfall glycoprotein
Table 96-6. CAUSES OF HYPOCITRURIC CALCIUM NEPHROLITHIASIS

<table>
<thead>
<tr>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal renal tubular acidosis</td>
</tr>
<tr>
<td>Complete</td>
</tr>
<tr>
<td>Incomplete</td>
</tr>
<tr>
<td>Chronic diarrheal syndrome</td>
</tr>
<tr>
<td>Thiazide-induced hypocitraturia</td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Diet high in animal protein</td>
</tr>
<tr>
<td>Strenuous physical exercise</td>
</tr>
<tr>
<td>High sodium intake</td>
</tr>
<tr>
<td>Active urinary tract infection</td>
</tr>
<tr>
<td>Intestinal malabsorption of citrate</td>
</tr>
</tbody>
</table>

Hyperuricosuria

- Defined as urinary uric acid $>600$ mg/day

- Up to 10% of calcium stone formers have high urinary uric acid levels as the only abnormality

- Hyperuricosuria increases urinary levels of monosodium urate, which in turn promotes calcium oxalate stone formation
Hyperuricosuria

- Uric acid may reduce the effectiveness of naturally occurring inhibitors of crystallization
  - Uric acid crystals can bind urinary GAGs that inhibit crystallization of calcium oxalate

- Frequency of uric acid stones in gout is about 20%

- Myeloproliferative disorders – acute leukemia etc are important causes of severe hyperuricosuria.
Uric acid stone

• 3 main factors of uric acid stone formation
  • Low pH
  • Low urine volume
  • Hyperuricosuria

Combination of these factors → crystallization of uric acid in the urine.
Uric acid stone

• 2 forms: free uric acid and urate salt, which forms a complex with sodium

• Sodium urate is 20X more soluble in water than free uric acid

• No known inhibitor of uric acid crystallization

• Rx: Urinary alkalization, diet change
Renal tubular acidosis (RTA)

• Results from defects in renal tubular $\text{H}^+$ secretion and urinary acidification

• 3 types of RTA: 1, 2 and 4
Type 1 RTA (distal)

- Most frequently associated with stone formation which occurs in up to 70% affected individuals
Type 1 RTA (distal)

• Characterized by
  • HypoK – due to the H\(^+\) retention and stimulus for H\(^+\) still present, the principal cells still pump out K\(^+\) and cause K wasting
  • HyperCa – due to the acidosis leeching out more Ca out of bone and the chronically elevated pH of urine leads to precipitation of calcium in urine leading to nephrolithiasis
  • Hypocitraturia - Profound hypocitraturia is the most important factor in stone formation due to impaired excretion as a result of met acidosis
80% reabsorbed

15% reabsorbed

5% excreted

100% \( \text{HCO}_3^- \)

Normal renal tubular function
Type 2 RTA (proximal)

- Primary defect – failure of HCO$_3^-$ absorption in the proximal tubule

- Results in increased urinary citrate excretion
Type 4 RTA

• Nephrolithiasis and nephrocalcinosis are uncommon because their calcium excretion is low

• A/W chronic renal damage – interstitial renal disease and diabetic nephropathy

• Commonly a/w aldosterone resistance
Struvite stones

- Composed of magnesium, ammonium and phosphate
- Accounts for 2 – 20% of all stones
- $F : M \rightarrow 2 : 1$
Struvite stones

- 2 criteria for crystallization of struvite
  - Urine pH 7.2 or above
  - Ammonia in the urine

- Urease-producing bacteria breaks down urea and releases ammonia (base) and carbonic acid (acid).

- Because 2 molecules of ammonia are produced from one molecule of urea, neutralization of the base is incomplete ➔ urinary pH ↑

\[
\text{CO(NH}_2\text{)}_2 + 2\text{H}_2\text{O} \xrightarrow{\text{Urease}} 2\text{NH}_3 + \text{H}_2\text{CO}_3
\]
<table>
<thead>
<tr>
<th>Commonest urease-producing pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Proteus</td>
</tr>
<tr>
<td>• Klebsiella</td>
</tr>
<tr>
<td>• Pseudomonas</td>
</tr>
<tr>
<td>• Staphylococcus</td>
</tr>
</tbody>
</table>

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Table 96–8. ORGANISMS THAT MAY PRODUCE UREASE

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Usually (&gt;90% of Isolates)</th>
<th>Occasionally (5%–30% of Isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteus rettgeri</td>
<td></td>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
<td></td>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td><strong>Proteus mirabilis</strong></td>
<td></td>
<td>Serratia marcescens</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td></td>
<td>Haemophilus parainfluenzae</td>
</tr>
<tr>
<td>Providencia stuartii</td>
<td></td>
<td>Bordetella bronchiseptica</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td></td>
<td>Aeromonas hydrophila</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td></td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td>Bacteroides corrodens</td>
<td></td>
<td>Pasteurella spp.</td>
</tr>
<tr>
<td>Yersinia enterocolitica</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brucella spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavobacterium spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td></td>
<td>Staphylococcus epidermidis</td>
</tr>
<tr>
<td>Micrococcus</td>
<td></td>
<td>Bacillus spp.</td>
</tr>
<tr>
<td>Corynebacterium ulcerans</td>
<td></td>
<td>Corynebacterium equi</td>
</tr>
<tr>
<td>Corynebacterium renale</td>
<td></td>
<td>Peptococcus asaccharolyticus</td>
</tr>
<tr>
<td>Corynebacterium ovis</td>
<td></td>
<td>Clostridium tetani</td>
</tr>
<tr>
<td>Corynebacterium hofmannii</td>
<td></td>
<td>Mycobacterium rhodochrous group</td>
</tr>
<tr>
<td>Mycoplasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T-strain Mycoplasma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureaplasma urealyticum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeasts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryptococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhodotorula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sporobolomyces</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candida humicola</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichosporon cutaneum</td>
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<td></td>
</tr>
</tbody>
</table>

Cystine stones

- Accounts for 1% of all urinary calculi
- Cystinuria – autosomal recessive disorder – failure of renal tubules in reabsorbing 4 basic amino acids – COLA
  - C – cystine
  - O – ornithine
  - L – lysine
  - A – arginine
- Only cysteine has poor solubility in urine
- Rx: High fluid intake, urinary alkalization (pH > 7), D-penicillamine
**Miscellaneous stones**

- **Xanthine** and Dihydroxyadenine stones
- Rare
- Can be confused with uric acid stones as both radiolucent
- Inherited disorder in the catabolic enzyme xanthine dehydrogenase or xanthine oxidase which catalyzes conversion of xanthine to uric acid
- Allopurinol, can also predispose to xanthine stones at very high levels.
Miscellaneous stones

- **Indinavir** stones
- Indinavir sulfate is a protease inhibitor, which has high urinary excretion and poor solubility at physiologic urinary pH
- May be invisible on Xray or CT
Miscellaneous stones

- **Guaifenesin** and **Ephedrine** – at risk of stones derived mainly from metabolites of these medicines
- Radiolucent on Xray, radiopaque on CT
Miscellaneous stones

• **Ammonium acid urate** stones – a/w laxative abuse, recurrent UTI, recurrent uric acid stone formation, and inflammatory bowel disease

• Laxative abuse leads to GI fluid loss causing intracellular acidosis and enhanced ammonia excretion. Because urinary sodium is very low with laxative use, urate complexes with abundant ammonia.
Anatomic Predisposition to Stones

- Ureteropelvic junction obstruction (UPJO) – incidence is nearly 20%

- Horseshoe kidneys
  - prevalence 0.25% with stone association 20%
  - Relative impairment of renal drainage, predisposing to UPJO. Stasis → stones

- Calyceal diverticula – associated with stones up to 40% patients

- Medullary sponge kidney
  - Ectasia of the renal collecting ducts
  - Nephrocalcinosis and renal calculi are frequent complications
Reference

• Campbell’s Urology, 10th edition