Update on the Medical Management of Urolithiasis

Or
Why do I form kidney stones and what can I do about it?

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Concord Hospital Center for Urologic Care
Objectives

• Introduce new concepts regarding stone formation
• Provide an overview of the medical evaluation of the stone former
• Highlight important medical and surgical risk factors for stone formation
• Discuss the medical management of the stone former
ESWL
Laser lithotripsy
PCNL
Technologic Advances are Wonderful!

BUT:

• Surgical treatments do not alter the course of the disease
• 10% prevalence in the US
• Recurrence after first stone:
  – Year 1: 10-15%
  – Year 5: 50-60%
  – Year 10: 70-80%
• $2.1 billion / year in 2000 (Pearle et al 2005)
• Fails to account for the lost wages, reduced work productivity
Prevalence of Kidney Stones by Age (Males)

- **1976-1980**
- **1988-1994**

Stamatelou, Kidney Int, 2003
Prevalence of History of Kidney Stones By Age (Females)

Stamatelou, Kidney Int, 2003
National Health and Nutrition Examination Survey

1994

2012

Men
Women

Scales Eur Urol 2012
Why do stones form?
Free Crystal Particle Growth

- Urine contains stone forming salts such as calcium and oxalate
- If these stay in solution, crystals do not form
- Crystals, which can become stones, form under certain circumstances
Factors That Promote Crystal Formation

• Concentration of stone forming salts
• pH
• Concentration of inhibitors
Pathophysiology: Supersaturation

Phenomena

- Nucleation will occur
- Crystal growth will occur
- Crystal aggregation will occur
- Inhibitors will impede or prevent crystallization
- De novo nucleation is very slow
- Heterogeneous nucleation may occur
- Matrix may be involved
- Crystals will not form
- Existing stones may dissolve

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Randall’s Plaque
Randall’s Plaque

Stone former

Normal
Randall’s Plaque

A

B
Attached Stone
Unattached Stone
Calcium Oxalate Stone Former
Calcium Oxalate Stone Former
Intestinal Bypass Patient
Intestinal Bypass Patient
Brushite Stone Former
Renal Medulla

Interlobar artery
Interlobar vein
Fenestrated ascending vasa recta
Juxtamedullary glomerulus
Descending vasa recta
Loop of Henle
Collecting duct
Vascular Etiology Theory
Evidence for Vascular Theory

• Epidemiologic
  – Association of atherosclerosis and hypertension with stones

• Clinical
  – Absence of stones with abnormal urinary studies and recurrent stones in spite of normal urinary studies

• Anatomical
  – Association of calcified vasculature with collecting tubules

• Physiological
  – Blood flow: laminar to turbulent and calcified vessels
Why do I form stones?

• Classic: Concentrations stone forming salts and inhibitors along with other factors such as urinary pH
• New: Complex pathophysiologic processes not fully understood in the renal medulla involving deposition of apatite at the tip of the papilla is the initial stone forming event
• New: Vascular pathology is the initial stone forming event
What can I do to prevent another attack?

• Improved diagnostic methods now uncover the underlying cause of stone disease in the vast majority of individuals

• Advances in selective therapy can reduce stone forming risk
Diagnostic Approach

- History and Physical
- Urine sediment
- Serum Chemistries
- Appropriate imaging
- 24 hour urine stone risk profile
History

- Prior stones and treatments
- Medical History: HTN, DM, Gout, others
- Prior GU surgery
- Prior GI surgery
- Bowel disease, fluid loss
- Stone-provoking medications
- Dietary factors
Medications

- Calcium and Vitamin D supplements
- Antacid and laxative use
- Lasix
- Vitamin C
- Topiramate
Minimal Diagnostic Tests

• Stone Analysis
• BMP
• Appropriate imaging
• Urinalysis
• 24 hour urine for Diagnostic Panel
Stone Composition

- Calcium containing: 75-80%
- Uric Acid: 10%
- Others: 10%
  - Struvite
  - Cystine
  - Sodium urate
  - Ammonium acid urate
24 Hour Urine

- Standardized, automated
- Volume recorded and aliquot sent to central lab
- Metabolic Factors (Ca, Ox, UA, citrate, pH)
- Environmental Factors (TV, Na, Sulfate, Phos, Mg)
- Physiochemical: Supersaturations
Values larger, bolder and more towards red indicate increasing risk for kidney stone formation.

### Summary Stone Risk Factors

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Decreased Risk</th>
<th>Increasing Risk for Stone Formation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine Volume (liters/day)</td>
<td></td>
<td>1.25</td>
</tr>
<tr>
<td>SS CaOx</td>
<td></td>
<td>9.85</td>
</tr>
<tr>
<td>Urine Calcium (mg/day)</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td>Urine Oxalate (mg/day)</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>Urine Citrate (mg/day)</td>
<td>523</td>
<td></td>
</tr>
<tr>
<td>SS CaP</td>
<td>1.30</td>
<td></td>
</tr>
<tr>
<td>24 Hour Urine pH</td>
<td>5.756</td>
<td></td>
</tr>
<tr>
<td>SS Uric Acid</td>
<td></td>
<td>1.68</td>
</tr>
<tr>
<td>Urine Uric Acid (g/day)</td>
<td>0.686</td>
<td></td>
</tr>
</tbody>
</table>

### Interpretation Of Laboratory Results

Urine volume has fallen and is very low (was 2.11 and now is 1.25 l/d). Low urine volume in a stone former should always be corrected if possible. A good clinical goal is 2.5 liters daily. Recheck in 6 weeks and adjust fluid intake as needed. The low urine volume is permitting a combined increase of SS CaP and SSUA.

Calcium oxalate stone risk (SS CaOx) has risen and is high (was 4.27 and now is 9.85). In general, urine calcium, oxalate, citrate, and volume are the main factors responsible. The graphic display indicates which are most deviated from normal. Management suggestions are as noted above.
Diagnostic Approach

1. Pathophysiological Exploration
2. Physicochemical Elucidation
   - Diagnostic Separation
     - Tailor-made Treatment
   - Dietary Aberrations
Calcium Stone Formation

- Hypercalciuria
- Hypocitraturia
- Hyperoxaluria
- Hyperuricosuria
Hypercalciuria

- Absorptive
- Renal
- Resorptive: Primary Hyperparathyroidism
Absorptive Hypercalciuria

Increased GI calcium absorption

Increased plasma Ca++

Decreased PTH

Increased urinary Ca++
Renal Hypercalciuria
“renal leak”

- Increased urinary calcium
- Decreased plasma Ca++
- Increased PTH
- Increased GI absorption
- Inc. Vit. D
- Increased bone resorption

Diagram showing renal anatomy with arrows indicating the flow of these processes.
Resorptive Hypercalciuria

“Primary Hyperparathyroidism”

Increased PTH

- Increased bone resorption
- Increased GI Ca++ absorption
- Increased plasma Ca++
- Increased urinary Ca++
Calcium Metabolism and Parathyroid Function

[Diagram showing the relationship between parathyroid hormone (PTH), calcium, kidney reabsorption, vitamin D, and phosphate levels with negative feedback mechanisms.]

- PTH increases calcium and phosphate levels.
- Calcium reabsorption from the kidney.
- Vitamin D increases 1,25 (OH)₂ vitamin D levels.
- Phosphate levels are regulated by a negative feedback mechanism.
## Bone Mineral Density and Hypercalciuria

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Measurement Method</th>
<th>Measurement Site</th>
<th>BMD Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lawoyin et al., 1979</td>
<td>SPA</td>
<td>Radius</td>
<td>↓ N</td>
</tr>
<tr>
<td>Fuss et al., 1983</td>
<td>SPA</td>
<td>Radius</td>
<td>↓</td>
</tr>
<tr>
<td>Pacifici et al., 1990</td>
<td>QCT</td>
<td>Spine</td>
<td>↓</td>
</tr>
<tr>
<td>Bataille et al., 1991</td>
<td>QCT</td>
<td>Spine</td>
<td>↓</td>
</tr>
<tr>
<td>Borghi et al., 1991</td>
<td>DPA</td>
<td>Spine</td>
<td>↓</td>
</tr>
<tr>
<td>Pietschmann et al., 1992</td>
<td>DEXA, SPA</td>
<td>Spine, radius</td>
<td>↓</td>
</tr>
<tr>
<td>Jaeger et al., 1994</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Weisinger et al., 1996</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Ghazali et al., 1997</td>
<td>QCT</td>
<td>Spine</td>
<td>↓</td>
</tr>
<tr>
<td>Giannini et al., 1998</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Misael da Silva et al., 2002</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Tasca et al., 2002</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Asplin et al., 2003</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Vezzoli et al., 2003</td>
<td>DEXA</td>
<td>Spine, femur</td>
<td>↓</td>
</tr>
<tr>
<td>Caudarella et al., 2003</td>
<td>DEXA, QUS</td>
<td>Radius, finger</td>
<td>↓</td>
</tr>
</tbody>
</table>

SPA = single photon absorptiometry; DEXA = dual energy x-ray absorptiometry; DPA = dual photon absorptiometry; QCT = quantitative computed tomography; QUS = quantitative ultrasonography; N = normal; ↓ = reduced.
Fig. 3. Observed (solid line) and expected (dashed line) cumulative incidence of vertebral fractures among Rochester, Minnesota, residents following the initial episode of symptomatic urolithiasis, 1950 to 1974.
Hypocitraturia

• Citrate is a well recognized inhibitor of stone formation
• Defined as <300 mg/day (arbitrary)
• 20-60% of calcium stone formers
Hypocitraturia

- Citrate is a well recognized inhibitor of stone formation
- Defined as <300 mg/day (arbitrary)
- 20-60% of calcium stone formers
Hypocitraturia
Pathogenesis

• Type I (Distal) RTA
• Chronic diarrheal states
• Excessive animal protein intake
• Thiazide induced hypokalemia
• Idiopathic
• Medication induced
Renal Tubular Acidosis: Clues to Diagnosis

• Young female with early age of onset
• Nephrocalcinosis
• Urine pH > 6.5
• Profound hypocitraturia
• Hyperchloremic, hypokalemic acidosis
• Stone composition: Calcium phosphate
Topiramate and Hypocitraturia
Hyperoxaluria

• Idiopathic
  – Most common
• Enteric
  – Intestinal disease/resection
  – Bariatric surgery
• Primary
  – rare
**Oxalate Production**

Dietary Oxalate
100 mg

GI Absorption
10 mg

Stool
90 mg

Glyoxalate

Ascorbic Acid

Endogenous Production
24 mg

Urinary oxalate
34 mg
Enteric Hyperoxaluria

- Should be suspected in any patient with hyperoxaluria and a small bowel abnormality
- 5% of patients in specialized metabolic stone clinics
- Low urine volume
- Low calcium, magnesium, citrate excretion
Bariatric Surgery

![Graph showing Urine Oxalate levels for different groups](image)

- **Normals**
- **Routine Stone-Formers**
- **Restrictive Bariatric**
- **RYGB Bariatric**

* P < 0.0001 vs. RYGB Bariatric group
# Bariatric Surgery and Stone Treatment

## Table 2. Summary of kidney stone procedures performed

<table>
<thead>
<tr>
<th>Procedure</th>
<th>RYGB Group</th>
<th>Control Group</th>
<th>p Value (chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shock wave lithotripsy</td>
<td>81 (1.75)</td>
<td>19 (0.41)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ureteroscopy with or without lithotripsy</td>
<td>98 (2.11)</td>
<td>27 (0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Percutaneous nephrolithotomy</td>
<td>6 (0.13)</td>
<td>3 (0.06)</td>
<td>0.5076*</td>
</tr>
<tr>
<td>Overall</td>
<td>153 (3.30)</td>
<td>43 (0.93)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Fisher’s exact test.

Matlaga, J. Urol 2009
Hyperuricosuria

• Arbitrarily defined as uric acid excretion exceeding 600 mg/day
• Independent risk factor for calcium oxalate stone formation
• Excess dietary purine intake is the most common cause
• Others include gout, myeloproliferative disorders, multiple myeloma, hemolytic disorders
Hyperuricosuric CaOx Lithiasis: Pathogenesis
Obesity and Stones

• Increasing incidence of stones has paralleled the increasing incidence of obesity
• Higher stone risk with increasing BMI
• Obesity closely associated with development of metabolic syndrome
• Higher risk of uric acid nephrolithiasis
Obesity Trends

Taylor, JAMA 2008
NHANES: Prevalence of Kidney Stones

Percent Prevalence

BMI Category

Normal
Overweight
Obese

Men
Women

0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Childhood Obesity
24 hour urine and Obesity

• Lower pH
• Lower citrate
• Higher oxalate
• Higher sodium and sulfate
• Higher uric acid
Diabetes and Stones

- DM (Type II) has been shown in population based studies to raise the risk of kidney stones
- Insulin resistance is the primary mechanism resulting in low urinary pH increasing uric acid stone risk
- Insulin resistance lowers urinary citrate thus increasing calcium stone risk
Prevalence of Uric Acid Lithiasis

Reported in Literature: 10%
Non-diabetic: 5%
Diabetic: 35%

Pak et al, Urol 2003
Pathogenesis of Uric Acid Lithiasis

- Uric acid nephrolithiasis
  - Low urine volume
  - Diarrheal states
  - Obesity ↔ Insulin resistance

- Low urinary pH
  - High animal protein diet
  - Myeloproliferative disorders

- Hyperuricosuria
  - Primary gout
  - Uricosuric medications
  - Congenital disorders

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Uric Acid Lithiasis: Pathogenesis
Uric Acid Lithiasis

- Increased acid load
- Reduced urinary $\text{NH}_4^+$
- pH decrease
- Inhibitor
- Urate → Uric Acid
Treatment: Dietary Modification

• Borghi et al, Nutrition Rev. July 2006, 301-312
• High Fluid Intake: Ten 10 oz. glasses H₂O/day or 2-2.5L urine/day
• Sodium Restriction: Keep salt intake to 2500 mg/day
• Oxalate restriction: oxalate rich foods and Vitamin C
• Adequate calcium rich foods
• Limit animal protein intake: 6 oz. servings
• Increase citrus fruit and juice intake
Medical Therapy: Rationale

• Many patients will have stone recurrence in spite of dietary modification
• Most stone formers have metabolic abnormalities that are not caused by, but are exacerbated by dietary indiscretions
• Many patients are poorly compliant with dietary modification
## 5510 · StoneRisk® Diagnostic Profile

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Environmental</th>
<th>Relative Supersaturation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca</td>
<td>Ox</td>
<td>UA</td>
</tr>
<tr>
<td>402 (≥ 250) mg/day</td>
<td>35 (&lt; 45) mg/day</td>
<td>748 (≥ 700) mg/day</td>
</tr>
</tbody>
</table>

### Other Values

- **NH₄**
  - 31 (14-62) mmol/d

- **K**
  - 102 (19-135) mmol/d

- **Creatinine**
  - 1950 (800-2000) mg/d
Thiazide Diuretics

- Patients with severe hypercalciuria (>275 mg/day)
- Patients with mild hypercalciuria and reduced bone mineral density
- Hypocalciuric action due to enhanced calcium reabsorption in the proximal renal tubule
Thiazides

- HCTZ 25-50 mg/BID
- Indapamide 1.25 – 2.5 mg/day
- Chlorthalidone 25 mg/day
  - K-Cit 40-60 meq/day
- Moduretic (amiloride + HCTZ) ½ tab BID
Thiazides
Potential Hazards

• Hypokalemia: closely monitor and use potassium supplements
• Hypocitraturia: monitor and use KCit supplements
• Hyperuricosuria: purine restriction, possibly use allopurinol
Hypocitraturia: Potassium Citrate

- Corrects hypocitraturia in patients with calcium oxalate stones
- Provides potassium supplementation for patients on thiazides
- Corrects hypocitraturia in patients with RTA
- Maintains pH between 6.0-6.5 in patients with uric acid stones
Potassium Citrate

- Liquids/crystals
  - Polycitra-K
  - Citra-K

- Slow release pills
  - Urocit K
## Potassium Citrate

<table>
<thead>
<tr>
<th></th>
<th>Liquid</th>
<th>Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor GI complaints</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Gastric erosions</td>
<td>0</td>
<td>0/+</td>
</tr>
<tr>
<td>Convenience</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Citraturic action</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Half-life</td>
<td>short</td>
<td>prolonged</td>
</tr>
<tr>
<td>Dose schedule</td>
<td>tid/qid</td>
<td>bid/tid</td>
</tr>
</tbody>
</table>
Allopurinol

- Used most appropriately in the recurrent calcium oxalate stone former with moderate to severe hyperuricosuria
- Failed dietary modification
- Dosed 200-300 mg/day
- Monitor liver enzymes
- Stephens-Johnson Syndrome: Report of skin rash or urticaria should prompt immediate cessation
Do Medications Work?
Thiazides

Pearle J Endourol 1999
Figure showing the proportion of stone-free patients over months for Potassium Citrate and Placebo groups. The Kaplan-Meier survival curve indicates a higher proportion of stone-free patients in the Potassium Citrate group compared to the Placebo group. The risk ratio (RR) is 0.25, with a 95% confidence interval (CI) of 0.09 - 0.70. Source: Barcelo, J Urol, 1993.
Table 5. Stone formation in 134 patients only on KCit

<table>
<thead>
<tr>
<th></th>
<th>Before KCit</th>
<th>After KCit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone formation rate change</td>
<td>1.22</td>
<td>0.19*</td>
</tr>
<tr>
<td>% Remission</td>
<td></td>
<td>72</td>
</tr>
<tr>
<td>% Decrease</td>
<td></td>
<td>94</td>
</tr>
<tr>
<td>% No change</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>% Increase</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

* Vs before KCit p < 0.0001.
Medical and Dietary Treatment and Bone Health

Pak, J Urol, 2003
BMD and Potassium Citrate

<table>
<thead>
<tr>
<th></th>
<th>Gm./Cm.$^2$</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.981 ± 0.131</td>
<td></td>
</tr>
<tr>
<td>Last</td>
<td>1.013 ± 0.133 (p &lt;0.05)</td>
<td>3.3 ± 4.2 (p &lt;0.01)</td>
</tr>
<tr>
<td><strong>Women:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.046 ± 0.070</td>
<td></td>
</tr>
<tr>
<td>Last</td>
<td>1.072 ± 0.080 (p &lt;0.05)</td>
<td>2.7 ± 1.7 (p &lt;0.05)</td>
</tr>
<tr>
<td><strong>Combined:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.997 ± 0.121</td>
<td></td>
</tr>
<tr>
<td>Last</td>
<td>1.027 ± 0.123 (p &lt;0.01)</td>
<td>3.1 ± 3.7 (p &lt;0.001)</td>
</tr>
</tbody>
</table>

*Significant difference from baseline to last measurement.
Take Home Points

• Research into Randall’s plaque formation is providing new insights into calcium stone formation

• A careful medical history and simple diagnostic evaluation will characterize most patient’s stone forming risk
Take Home Points

• Obesity and metabolic syndrome are important risk factors for stone formation
• Type 2 DM is an important risk factor for stone formation
• Bariatric surgery is an important and increasing cause of stone formation
• Dietary modification can help lower stone forming risk
Take Home Points

• For many stone formers, genetic and medical risk factors will limit the effectiveness of diet changes alone

• For these patients, medical therapy is available and effective in reducing stone forming risk and in preventing complications of stones such as bone loss

• Kidney stone formation is often a reflection of a systemic medical/metabolic syndrome