Urinary Calculus Disease

Incidence: 7-21/10,000
3 men: 1 woman
Peak age of onset: 20-30 years
Morbidity > Mortality

Urinary Calculus Disease

Five major stone types:
- Calcium oxalate: Monohydrate / Dihydrate
- Calcium phosphate: Brushite / Apatite
- Struvite: Infection stones
- Uric acid: pH < 5.5
- Cystine: SLC 3a1
Urinary Calculus Disease

Struvite
- Infection stone
- Magnesium ammonium phosphate
- pH always > 7.2
- Woman much more common than men
- Urease producing organisms
- Rarely present with ureteral stones/colic
  without prior manipulation

Urinary Calculus Disease

Uric acid
- pH < 5.5
- Radiolucent
- Men > women
- Medical dissolution -- increased pH
- Effective prophylaxis -- increased pH
- High recurrence rate without medications

Urinary Calculus Disease

Cystine
- Ground glass radiographic appearance
- Smooth edges
- Frustrating recurrence despite medical therapy
  - Thiola - disulfide binder
  - Urinary alkalinization
### Urinary Calculus Disease

**General dietary recommendations**
- Decrease sodium intake
  - Eliminate salt shaker at table
  - Assess sodium when shopping
  - Eating out increases sodium intake
- Decrease animal protein intake
- Oral fluid intake adequate to void 1.5 L/day

---

### Urinary Calculus Disease

- Hypercalciuria
- Hyperuricosuria
- Hyperoxaluria
- Hypocitraturia

---

### Calcium Nephrolithiasis

<table>
<thead>
<tr>
<th>Hypercalciuria</th>
<th>Hyperuricosuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorptive</td>
<td>Endogenous</td>
</tr>
<tr>
<td>Resorptive</td>
<td>Dietary excess</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypocitraturia</th>
<th>Hyperoxaluria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Primary</td>
</tr>
<tr>
<td></td>
<td>Enteric</td>
</tr>
</tbody>
</table>
PATIENT HC

• PAST UROLOGIC HISTORY
  – Left SWL 2001
  – Left URS with laser lithotripsy ‘03, ‘05
  – No history of metabolic stone workup

• FAMILY HISTORY
  – Mother with stones (no surgery)
  – Brother with stones s/p SWL

PATIENT HC

• ROS
  – negative

• PMH
  – diabetes mellitus
  – hypertension
  – obesity
  – angina s/p cardiac stent in 2007

• MEDICATIONS
  – glyburide
  – lisinopril
  – HCTZ
  – aspirin
PATIENT HC

• SOCIAL HISTORY
  – married
  – 2 children
  – emigrated from Japan 25 years ago
  – owns local bookstore
  – 20 pack year tobacco history
  – social EtOH
  – sleeps left side down

PATIENT HC

• PE
  – 5’3” tall, 183 lbs
  – BMI = 32.4
  – BP 146/88, HR 75
  – Abdomen soft, non-tender, non-distended, healed percutaneous puncture site

• KUB
  – no residual stones

FURTHER WORKUP?
TRADITIONAL WORKUP

- Serum studies
  - Parathyroid hormone
  - Uric acid
  - Calcium
  - Electrolytes, BUN / creatinine
- 24-hour urinalysis (for recurrent stones)

Historical thinking – treat abnormalities found on serum and urine studies

WHAT HAVE WE LEARNED ABOUT METABOLIC STONE DISEASE IN THE PAST 10 YEARS???

SYSTEMIC DISEASE IS A RISK FACTOR FOR NEPHROLITHIASIS

AND (PERHAPS EQUALLY IMPORTANT)…

NEPHROLITHIASIS IS A RISK FACTOR FOR SYSTEMIC DISEASE
RISK FACTORS FOR NEPHROLITHIASIS

• Hypertension, diabetes mellitus
• Obesity, metabolic syndrome
• Gender
• ? Sleep position
• ? History of angina and atherosclerosis
• ? Family history of stones
• ? Race

HYPERTENSION

• Epidemiologic evidence

• Patients with hypertension are at risk for stones

• Stone-formers are at risk for hypertension

If you have hypertension…

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Follow-up</th>
<th>RR of stones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cappuccio</td>
<td>503 men</td>
<td>8 yr f/u</td>
<td>1.89 (1.12-3.18)</td>
</tr>
<tr>
<td>Borghi</td>
<td>260 men</td>
<td>8 yr f/u</td>
<td>5.5 (1.82-16.66)</td>
</tr>
</tbody>
</table>

If you have nephrolithiasis…

<table>
<thead>
<tr>
<th>Study</th>
<th>Gender</th>
<th>Follow-up</th>
<th>RR of HTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Madore</td>
<td>51,529 men</td>
<td>&gt; 15 yr f/u</td>
<td>1.29 (1.12-1.41)</td>
</tr>
<tr>
<td>Madore</td>
<td>89,376 women</td>
<td>&gt; 15 yr f/u</td>
<td>1.24 (1.13-1.37)</td>
</tr>
</tbody>
</table>

WHY DO HYPERTENSIVES FORM STONES?

• Proposed mechanisms
  – hypertensive subjects leak calcium from nephron\textsuperscript{1}
  – hypertensive subjects excrete less citrate\textsuperscript{2}
    more uric acid\textsuperscript{3}
    more oxalate\textsuperscript{4}
  – increased dietary sodium intake\textsuperscript{5,6}

\textsuperscript{1}Strazullo (1995), \textsuperscript{2}Taylor (1998), \textsuperscript{3}Tisler (2002), \textsuperscript{4}Borghi (1999), \textsuperscript{5}Muldowney (1982), \textsuperscript{6}Androgue (1978)

WHY DO STONE-FORMERS BECOME HYPERTENSIVE?

• Proposed mechanisms
  – nephrolithiasis leads to renal damage
    • obstructive uropathy\textsuperscript{1}
  – direct injury to tubular epithelial cells\textsuperscript{2}

\textsuperscript{1}Gambaro (2001), \textsuperscript{2}Knoll (2004)

DIABETES MELLITUS

• Epidemiologic evidence

• Women with diabetes mellitus are at risk for stones

• Stone-formers are at risk for diabetes mellitus
DIABETES MELLITUS

• If you have diabetes, incident stone risk is...
  - Older women 1.29 (1.05-1.58)
  - Younger women 1.60 (1.16-2.21)
  - Men 0.81 (0.59-1.09)

• If you have nephrolithiasis, incident diabetes risk is...
  - Older women 1.33 (1.18-1.50)
  - Younger women 1.48 (1.14-1.91)
  - Men 1.49 (1.29-1.72)

WHY DO DIABETICS FORM STONES?

• Proposed mechanisms
   - increased uric acid production
   - decreased urine pH
   - impaired renal ammonium production from insulin resistance
   - elevated serum glucose
   - decreased renal calcium reabsorption
   - increased filtered calcium

DIABETES AND 24-HOUR URINE CHEMISTRIES AT UCSF

<table>
<thead>
<tr>
<th>Substance</th>
<th>Coef (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>20.7 (1.8 – 39.4)</td>
</tr>
<tr>
<td>Calcium</td>
<td>-15.9 (-46.4 – 14.6)</td>
</tr>
<tr>
<td>Citrate</td>
<td>57.9 (-54.7 – 167.5)</td>
</tr>
<tr>
<td>Uric acid</td>
<td>0.02 (-0.02 – 0.1)</td>
</tr>
<tr>
<td>Oxalate</td>
<td>6.1 (0.9 – 11.3)</td>
</tr>
<tr>
<td>Potassium</td>
<td>-2.6 (-9.7 – 4.5)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>-0.1 (-0.2 – -0.004)</td>
</tr>
<tr>
<td>Magnesium</td>
<td>-0.03 (-11.0 – 11.1)</td>
</tr>
<tr>
<td>Sulfate</td>
<td>-0.9 (-4.5 – 2.6)</td>
</tr>
<tr>
<td>pH</td>
<td>-0.3 (-0.5 – -0.02)</td>
</tr>
<tr>
<td>Volume</td>
<td>0.4 (0.1 – 0.6)</td>
</tr>
<tr>
<td>SS CaOx</td>
<td>0.02 (-0.9 – 1.0)</td>
</tr>
<tr>
<td>SS CaP</td>
<td>0.2 (-0.05 – 0.4)</td>
</tr>
<tr>
<td>SS Ua</td>
<td>-0.03 (-0.2 – 0.1)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>-74.6 (-153.6 – 4.4)</td>
</tr>
</tbody>
</table>

Multivariate linear regression
469 stone-forming patients
Adjusted for age, gender, race, diet, hypertension, obesity, thiazide and K-Citrate use
DOES SWL “CAUSE” HYPERTENSION AND DIABETES

- Retrospective questionnaire review
  SWL versus ureteroscopy \(^1\)

- Increased HTN and diabetes in SWL group

- Question: cause or effect?

Krambeck (2006)

OBESITY

- Epidemiologic evidence

- Obesity increases risk of nephrolithiasis

- Increasing BMI increases risk of nephrolithiasis

- Weight gain increases risk of nephrolithiasis (but weight loss does not reduce risk)

Taylor (2005)

OBESITY

- Weight and incidence of stones

- < 150 lbs versus > 220 lbs
  - Older women RR 1.92 (1.59-2.31)
  - Younger women RR 1.89 (1.52-2.36)
  - Men RR 1.44 (1.11-1.86)
OBESITY
• BMI and incidence of stones
• < 21 versus ≥ 30
  – Older women RR 2.09 (1.77-2.48)
  – Younger women RR 1.90 (1.61-2.25)
  – Men RR 1.33 (1.08-1.63)

Taylor (2005)

OBESITY
• Weight change and incidence of stones
• 35 pound weight gain
  – Older women RR 1.82 (1.50-2.21)
  – Younger women RR 1.70 (1.40-2.06)
  – Men RR 1.39 (1.14-1.70)
• No change in risk with weight loss

Taylor (2005)

OBESITY AND 24-HOUR URINE CHEMISTRIES
• BMI ≥ 30 associated with
  lower urine pH
  hyperuricosuria hypocitraturia
• Highest quintile of BMI associated with
  increased urine oxalate
  Increased urine uric acid
  Increased urine sodium

OBESITY AND 24-HOUR URINE CHEMISTRIES

- Obese men and women versus their “non-obese” counterparts
  - Increased sodium
  - Increased calcium
  - Increased oxalate
  - Increased uric acid
  - Increased citrate
  - Decreased pH


OBESITY AND 24-HOUR URINE CHEMISTRIES AT UCSF

- Multivariate analysis of relationship between BMI and urine chemistries, stratified by age and gender

<table>
<thead>
<tr>
<th>Older women</th>
<th>Older men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing urine sodium</td>
<td>Increasing urine sodium</td>
</tr>
<tr>
<td>Decreasing urine calcium</td>
<td>Decreasing urine pH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Younger women</th>
<th>Younger men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing urine sodium</td>
<td>Increasing urine sodium</td>
</tr>
<tr>
<td>Increasing urine uric acid</td>
<td>Increasing urine citrate</td>
</tr>
<tr>
<td>Decreasing urine pH</td>
<td>Decreasing urine calcium</td>
</tr>
</tbody>
</table>

Eisner BH, Eisenberg ML, Stoller ML (submitted, 2009)

WHY DO OBESE PATIENTS FORM STONES?

- Proposed mechanisms
  - Insulin resistance leads to changes in urine chemistries
    - Oxalate
    - Calcium
    - Uric acid
    - pH

Powell (2000), Eisner (submitted 2009)
OBESITY AND 24-HOUR URINE CHEMISTRIES AT UCSF

Multivariate linear regression
469 stone-forming patients
Adjusted for age, gender, race, diet, hypertension, diabetes, thiazide and K-Citrate use

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lower CI</th>
<th>Upper CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>40.1</td>
<td>53.4</td>
</tr>
<tr>
<td>Calcium</td>
<td>-10.5</td>
<td>11.8</td>
</tr>
<tr>
<td>Citrate</td>
<td>17.3</td>
<td>97.5</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxalate</td>
<td>-1.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Potassium</td>
<td>0.05</td>
<td>5.6</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>Magnesium</td>
<td>-1.87</td>
<td>6.2</td>
</tr>
<tr>
<td>Sulfate</td>
<td>-3.7</td>
<td>-1.1</td>
</tr>
<tr>
<td>pH</td>
<td>-0.2</td>
<td>-0.01</td>
</tr>
<tr>
<td>Volume</td>
<td>136.8</td>
<td>195.1</td>
</tr>
<tr>
<td>SScA0X</td>
<td>0.05</td>
<td>0.8</td>
</tr>
<tr>
<td>SScAP</td>
<td>-0.01</td>
<td>0.2</td>
</tr>
<tr>
<td>SSUA</td>
<td>-0.08</td>
<td>0.2</td>
</tr>
<tr>
<td>Creatinine</td>
<td>136.8</td>
<td>195.1</td>
</tr>
</tbody>
</table>

OBESITY IS ASSOCIATED WITH INCREASED SODIUM AND DECREASED URINE pH

METABOLIC SYNDROME

- Metabolic syndrome
  - 3 of the following required
    - diabetes mellitus
    - hypertension
    - obesity
    - increased serum triglycerides
    - decreased serum HDL

METABOLIC SYNDROME

- Epidemiologic evidence

- Patients with metabolic syndrome are at risk for stones

- Stone-formers are at risk for metabolic syndrome
METABOLIC SYNDROME

• NHANES III - > 13,000 Americans

• Risk of nephrolithiasis increases with # of metabolic syndrome traits
  • 1 trait – RR 1.27 (0.77-2.10)
  • 3 traits – RR 1.76 (1.08-2.85)
  • 5 traits – RR 1.93 (1.04-3.56)

West (2009)

METABOLIC SYNDROME

• 2,132 men and women from S. Italy
  – Patients with hypertension are at increased risk of nephrolithiasis
  – Risk is greater in patients with obesity PLUS hypertension suggesting additive effects¹

Redina (2009)

METABOLIC SYNDROME

• CARDIA Study – 5,115 Americans, recruited at age 18-30 in 1985-1986, followed for 20 years
  • Multivariate analysis adjusting for age, gender, race, tobacco, and education
  • Nephrolithiasis predicts incidence of metabolic syndrome
    • $\beta = 1.89$ (95% CI 1.30-2.78), $p=0.001$

Eisner, Reiner, Jacobs, Kahn, Stoller (unpublished data)
FAMILY HISTORY

• Studies on “rare genetic diseases”
  – cystinuria
    • SLC3A1, SLC3A9
  – X-linked nephrolithiasis (Dent’s disease)
    • CLCN5

FAMILY HISTORY

• 1 large study in the literature looking at nephrolithiasis in twins

  • Proband concordance for nephrolithiasis
    monozygotic (MZ) twins 32%
    dizygotic (DZ) twins 17%

  • Tetrachoric analysis - Heritability risk for nephrolithiasis 56%

FAMILY HISTORY

• Hospitalization rates for nephrolithiasis in Danish Twin Study (30,000 twin pairs)

  • Proband concordance
    monozygotic twins 13.6%
    dizygotic twins 2.2%
    p <0.001
RACE (ASIAN vs. WHITE)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercalciuria</td>
<td>1.04 (0.50 - 2.12)</td>
</tr>
<tr>
<td>Hyperoxaluria</td>
<td>0.92 (0.50 - 1.70)</td>
</tr>
<tr>
<td>Hypocitraturia</td>
<td>2.33 (1.28 - 4.34)</td>
</tr>
<tr>
<td>Hyperuricosuria</td>
<td>5.56 (2.57 - 12.40)</td>
</tr>
<tr>
<td>Urine pH &lt; 5.8</td>
<td>1.66 (0.85 - 3.28)</td>
</tr>
<tr>
<td>SSCaOx &gt; 10</td>
<td>1.12 (0.46 - 2.67)</td>
</tr>
<tr>
<td>SSCaP &gt; 2</td>
<td>1.25 (0.44 - 3.51)</td>
</tr>
<tr>
<td>SSUA &gt; 1</td>
<td>7.02 (1.23 - 47.7)</td>
</tr>
</tbody>
</table>

Eisner, Porten, Bechis, Stoller (unpublished data)

Multivariate logistic regression
462 stone-forming patients
Adjusted for age, gender, diet, HTN, diabetes, BMI, thiazide and K-Citrate use

Asian race increases risk of
Hypocitraturia
Hyperuricosuria
• Increased uric acid supersaturation
(white race is referent)

Could the vascular system be involved in stone formation???
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

Alexander Randall
Stones related
Calcifications beneath papillary epithelium
Specifically: calcified basement membrane of collecting ducts
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

[Image of anatomical diagram]

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

[Image of microscopic view]

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

[Image of another microscopic view]
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

Intimate association between the collecting ducts and the papillary vasa recta

Is the primary stone event a vascular or uriniferous phenomenon?

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

Sleep for 6-12 hours / day
Normal subjects sleep for prolonged periods in lateral decubitus position
Younger patients move less

POSTURE AND MAG-3 RENAL PERFUSION

<table>
<thead>
<tr>
<th>Posture</th>
<th>Left Side</th>
<th>Right Side</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>51.9%</td>
<td>48.1%</td>
</tr>
<tr>
<td>Left side down</td>
<td>61.3%</td>
<td>38.7%</td>
</tr>
<tr>
<td>Right side down</td>
<td>36.7%</td>
<td>63.3%</td>
</tr>
</tbody>
</table>
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

• Is the initiating stone event vascular in origin?
• Electron microscopy shows that cells of renal papilla, where stones are often attached are associated with capillaries
• Biopsy of Randall’s plaques shows crystal deposits in vasa rectae of renal papilla

If the initial stone event is vascular in origin, then stone formers should be at increased risk for developing other systemic vascular conditions.

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

• Health Professionals Follow-up Study (HPFS)
• Prospective study of ~50,000 MEN
• Determine whether nephrolithiasis is an independent risk factor for vascular disease
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

- 20 year follow-up
  biennial questionnaires
- Multivariate analysis comparing risk of incident myocardial infarction coronary surgery or revascularization in men +/− a history of nephrolithiasis

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

<table>
<thead>
<tr>
<th></th>
<th>No nephrolithiasis</th>
<th>Nephrolithiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total person years</td>
<td>561,404</td>
<td>64,575</td>
</tr>
<tr>
<td>Number of cases</td>
<td>4150</td>
<td>470</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1712</td>
<td>200</td>
</tr>
<tr>
<td>Coronary artery bypass graft</td>
<td>2905</td>
<td>333</td>
</tr>
<tr>
<td>Total coronary heart disease</td>
<td>4710</td>
<td>463</td>
</tr>
</tbody>
</table>

Eisner, Cooperberg, Curhan, Stoller (2007)

NEPHROLITHIASIS IN MEN IS ASSOCIATED WITH INCREASED RISK OF
- MYOCARDIAL INFARCTION
- CORONARY REvascularization

VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

- Study of Osteoporotic Fractures (SOF)
- Prospective study of ~10,000 WOMEN
- Determine whether nephrolithiasis is an independent risk factor for vascular disease
VASCULAR IMPLICATIONS OF URINARY STONE DISEASE

- Baseline medical questionnaires
- Multivariate analysis comparing risk of prevalent Myocardial infarction Angina Congestive heart failure Cardiovascular mortality in women +/- a history of nephrolithiasis

NEPHROLITHIASIS IN WOMEN IS ASSOCIATED WITH INCREASED PREVALENT • MYOCARDIAL INFARCTION • ANGINA • CONGESTIVE HEART FAILURE • BUT NOT MORTALITY

NEPHROLITHIASIS AND CORONARY ARTERY CALCIUM

- CARDIA Study – 5,115 Americans, recruited at age 18-30 in 1985-1986, followed for 20 years
- Linear regression model
- Nephrolithiasis is associated with increasing CAC (Coronary Artery Calcification) score
- $\beta = 1.77$ (95% CI 1.20-2.60), $p=0.004$

Eisner, Stone, Cooperberg, Kahn, Stoller (2009)
NEPHROLITHIASIS AND CAROTID ARTERY THICKNESS

- Multivariate model adjusting for age, gender, race, tobacco use, DM, BMI
- Nephrolithiasis is associated with increasing carotid artery wall thickness
- $\beta = 0.136$ (95% CI 0.012-0.26), $p=0.03$

NEPHROLITHIASIS IS ASSOCIATED WITH INCREASED CORONARY ARTERY CALCIUM INCREASED CAROTID ARTERY WALL THICKNESS

TAKE HOME MESSAGES

- Etiology of nephrolithiasis is incompletely understood
- Traditional theories of abnormal urine chemistries do not fully explain stone disease
- Need to get "beyond the 24-hour urine" to fully understand patients with nephrolithiasis
TAKE HOME MESSAGES

• Recent evidence linking nephrolithiasis to systemic disease (hypertension, diabetes, obesity)
• New research shows accumulating epidemiologic and anatomic evidence for vascular etiology of urinary stones
• May have an impact on future therapy

A STONE IS A STONE...

OR MAYBE IT ISN’T!!!