A Simplified Approach to the Metabolic Evaluation of the Stone Former

(Referencing the AUA Medical Management of Kidney Stones Guideline)

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Classification of Stone Causes

Infection

Struvite

Carbonate apatite

Matrix

Metabolic

Calcium

Calcium Oxalate

Calcium Phosphate

Uric Acid

Cystine

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When should a metabolic evaluation be considered?

- Recurrent stone disease
- Stone burden requiring invasive surgery
- Solitary kidney
- Family history
- Skeletal conditions (osteoporosis, fracture)
- Inflammatory bowel disease / bowel surgery
- Children

What is the rationale for a metabolic evaluation?

- The clinical stone may be the phenotypic expression of an underlying metabolic abnormality

- We can identify and mitigate these abnormalities

All pts with a newly diagnosed stone should undergo a screening evaluation (Clinical Principle)

What is the optimal timing of the 24 hour urine collection?

- Presence of stone material in collecting system will not affect results
- Ideally should be done 1 month following an intervention
  - When patient has resumed normal lifestyle

Clinicians should obtain metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers (Standard: Grade B)

24-hr urine testing can be used to inform and monitor treatment regimens

Practical Evaluation of the Metabolic Stone Former
Calcium or Uric Acid Stones

- What tests can most hospitals perform?
  - 24 hour urine collections for:
    - Total volume
    - Calcium
    - Oxalate
    - Citrate
    - Uric Acid
    - Creatinine
    - Sodium
    - pH

Metabolic testing should consist of 1 or 2, 24-hr urine collections obtained on a random diet (Expert Opinion)

Practical Evaluation of the Metabolic Stone Former
Calcium or Uric Acid Stones

- What tests can most hospitals perform?
  - 24 hour urine collections for:
    - Total volume
    - Calcium
    - Oxalate
    - Citrate
    - Uric Acid
    - Creatinine
    - Sodium
    - pH
- Commercial vendors simplify the process
  - LithoLink
  - Mission Pharmacal

Calcium Stone Disease
The Hypercalciurias

- Metabolic classification
  - Absorptive hypercalciuria
  - Renal hypercalciuria
  - Resorptive hypercalciuria
    - 1° hyperparathyroidism

Clinicians should not routinely perform "fast and calcium load" testing to distinguish among types of hypercalciuria. (Recommendation: Grade C)

Absorptive Hypercalciuria

- Increased intestinal absorption of calcium
  - Type I – Occurs regardless of dietary calcium intake
  - Type II – Does not occur with calcium restriction
    - Different types likely only of academic interest
- Results in increased filtered calcium load and decreased renal reabsorption
- Excess renal losses preserve calcium homeostasis (zero sum balance)

Renal Hypercalciuria

- Impaired renal tubular calcium reabsorption
- Loss of calcium triggers parathyroid function
  - Mobilizes calcium from bone
  - Enhances GI absorption of calcium
- Increases renal filtered load of calcium

Resorptive Hypercalciuria

- Primary hyperparathyroidism
  - Hypersecretion of PTH
    - Excessive bone resorption
    - Increased GI calcium absorption
  - Results in increasing circulating calcium and increased renal filtered load of calcium

How to Treat Hypercalciuria

Thiazide Diuretics

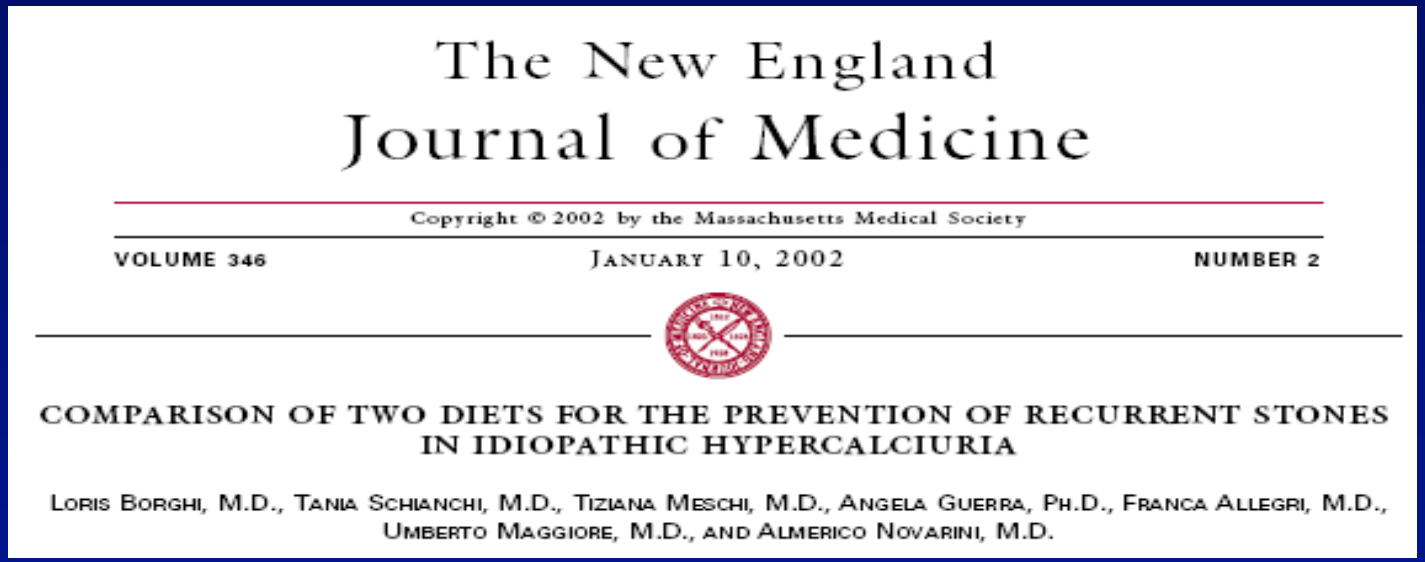
- Increases tubular calcium reabsorption
  - Distal tubule
  - Proximal tubule
- Requires potassium supplementation to prevent:
  - Hypokalemia
  - Hypocitraturia

Thiazide Diuretics

- Absorptive hypercalciuria
  - Will reduce calcium excretion
  - Retained calcium stored in bone
- Renal hypercalciuria
  - Ideal treatment
  - Corrects the renal leak
- Resorptive hypercalciuria
  - Not appropriate treatment of 1º hyperparathyroidism
    - May exacerbate hypercalcemia

Clinicians should offer thiazide diuretics to patients with high or relatively high urine calcium and recurrent calcium stones (Standard: Grade B)

Dietary Calcium Counseling



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COMPARISON OF TWO DIETS FOR THE PREVENTION OF RECURRENT STONES IN IDIOPATHIC HYPERCALCIURIA

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- Prospective, randomized study
  - 400 mg calcium diet
  - 1200 mg calcium diet
- Primary outcome - time to first stone
- Results at 5 year follow-up
  - Low calcium diet– 38% recurrence
  - Normal calcium diet – 20% recurrence

Sodium Restriction

- Dietary sodium can influence renal calcium excretion
  - Increase of 100 mEq/day of sodium will increase urinary calcium by 50 mg/day
  - Excess dietary sodium will attenuate hypocalciuric effect of thiazides

Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1000-1200 mg/d of dietary calcium (Standard: Grade B)

Calcium Supplements

- Can promote hypercalciuria
  - Especially at initiation of therapy
  - Magnitude of effect is variable
- What is recommended?

- Calcium citrate
  - No significant effect on CaOx/CaP supersaturation
  - Check 24 hour urine calcium following initiation
    - If elevated, can begin thiazide treatment
- What about Vitamin D?
  - No definitive evidence yet
  - There are health benefits from normalizing Vitamin D
    - Repletion is probably ok

The Hyperoxalurias

Idiopathic hyperoxaluria

Enteric hyperoxaluria

Primary hyperoxaluria

All associated with calcium oxalate stone disease

Idiopathic Hyperoxaluria

- Most common type of hyperoxaluria
- Initial treatment is dietary modification
  - Refrain from high oxalate foods
    - Ascorbate (Vitamin C) megadoses
  - Limit animal protein consumption
    - May increase oxalate excretion
  - Normal dietary calcium intake
    - Will reduce oxalate excretion

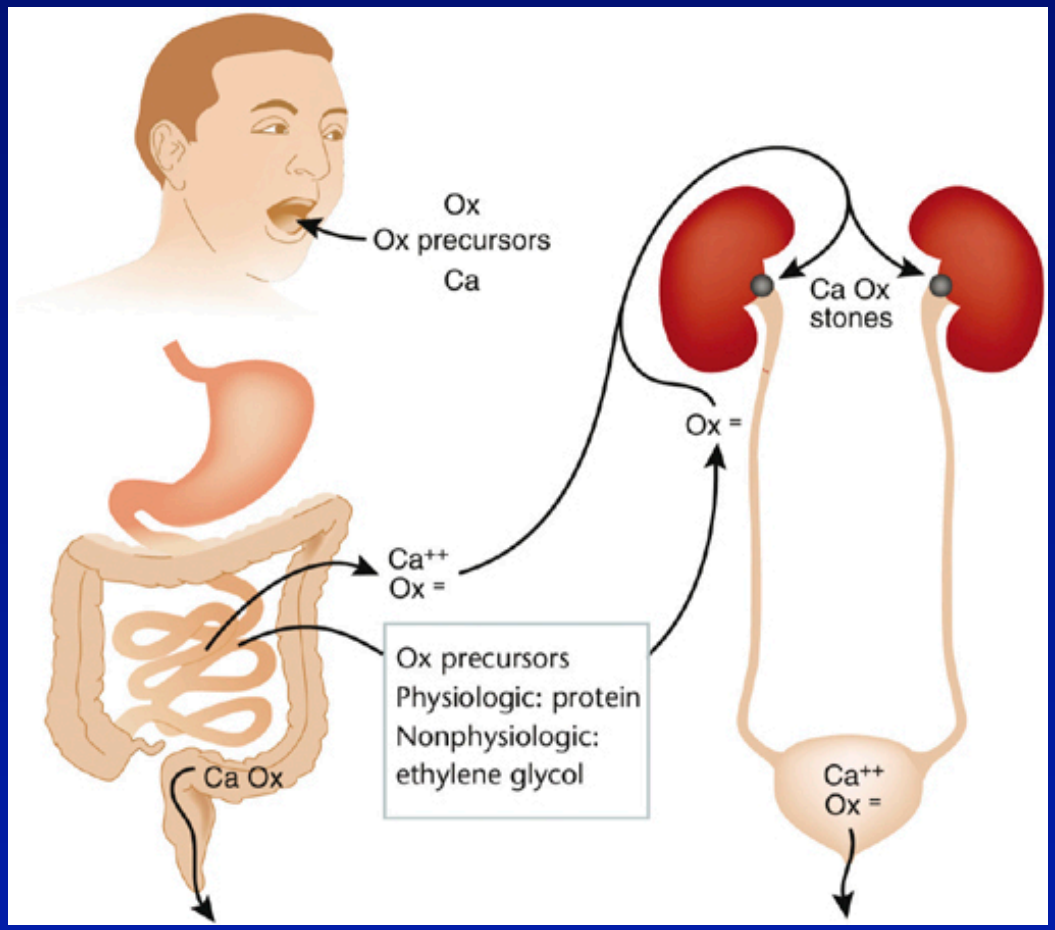
Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption. (Expert Opinion)

Enteric Hyperoxaluria

- Fat is malabsorbed
  - Ordinarily little fat reaches the colon
- In malabsorptive states fatty acids reach colon and bind calcium
  - Calcium normally binds oxalate in gut
  - Once complexed to fatty acids, calcium is unable to bind oxalate
  - Increased oxalate load absorbed and delivered to kidney
  - Urinary oxalate rises
  - Calcium oxalate stones form

Enteric Hyperoxaluria

Suspect with hyperoxaluria and bowel disease



Enteric Hyperoxaluria

- Other associated lithogenic factors
  - Low urine volume
    - Increased intestinal fluid losses
  - Hypocitraturia
    - Metabolic acidosis due to bicarbonate losses
    - Hypokalemia
  - Hypomagensiuria
    - Poor intestinal magnesium absorption

Enteric Hyperoxaluria

- Treatment
  - Correction of bowel pathology if possible
  - Increased fluid consumption
  - Low fat, low oxalate diet
  - Calcium citrate substitution
    - Promotes enteric calcium oxalate complexation
  - Magnesium supplementation
    - Will complex with oxalate
  - Cholestyramine
    - Will bind fatty acids, bile acids, oxalate
  - Potassium citrate
    - Correct underlying acidosis and hypokalemia

The Effect of Citrate

Citrate

- Citrate
  - Inhibitor of calcium oxalate stone formation
  - Forms soluble complexes with calcium
  - Inhibits crystallization of calcium salts
- Low urinary citrate seen in:
  - 5-10% of patients as isolated finding
  - 50% of patients as one of multiple finding
- Can be repleted with potassium citrate

Etiology of Hypocitraturia

- Idiopathic
- Distal Renal Tubular Acidosis (Type I)
- Chronic Diarrheal States
- Thiazide-induced
- UTI
  - Loss of citrate lyase

- Really, any state with a metabolic acidosis
  - Decreases renal citrate synthesis
  - Increases renal citrate reabsorption

Etiology of Hypocitraturia

- Idiopathic
- Distal Renal Tubular Acidosis (Type I)

Clinicians should offer potassium citrate therapy to patients with recurrent calcium stones and low or relatively low urinary citrate (Standard: Grade B)

  - GI
  - Loss of citrate lyase

- Really, any state with a metabolic acidosis
  - Decreases renal citrate synthesis
  - Increases renal citrate reabsorption

Uric Acid Stones

- Accounts for 5-10% of all stones
- Most common in patients with no obvious uric acid metabolism abnormality
  - Associated with certain uric acid disorders, though
    - Purine gluttony
    - Metabolic syndrome (insulin resistance)
    - Gouty diathesis
- Also associated with:
  - Chronic diarrheal states
  - Myeloproliferative disorders

Uric Acid Stones

- Pathogenesis
  - Increased urinary uric acid is helpful, but not mandatory
  - Relatively acidic urine pH is **required**

$$H^+ + Urate^- \leftrightarrow \text{Uric Acid}$$

    - Low pH drives soluble urate salt to insoluble uric acid
    - pKa of uric acid is 5.75

Treatment of Uric Acid Calculi

- Increase urinary pH with alkali therapy
  - Potassium citrate
    - Generally begin at 20-30 mEq BID dosing
    - Follow urinary pH
      - At pH 6.5 most uric acid will be soluble
- If hyperuricosuria is present:
  - Allopurinol will decrease uric acid production
    - Blocks ability of xanthine oxidase to convert xanthine to uric acid
- Dietary purine reduction

Treatment of Uric Acid Calculi

- Increase urinary pH with alkali therapy
  - Potassium citrate

Clinicians should offer potassium citrate to patients with uric acid and cystine stones to raise urinary pH to an optimal level. (Expert Opinion)

- If hyperuricosuria is present:
  - Allopurinol will decrease uric acid production
    - Blocks ability of xanthine oxidase to convert xanthine to uric acid

Clinicians should *not* routinely offer allopurinol as first-line therapy to patients with uric acid stones (Expert Opinion)

Pharmacologic Take Home Points

- Hypercalciuria

  (Absorptive or renal leak – both treated the same)

  – Managed with thiazides / potassium supplement
    - HCTZ or chlorthalidone or indapamide
    - Potassium citrate 10-20 mEq q D

      or (if stone composition is calcium phosphate)
    - Potassium chloride 10-20 mEq q D
  – Check BMP 2-3 days after starting therapy
  – Check 24 hour study 3-4 weeks later

Pharmacologic Take Home Points

- Hypocitraturia
  - Replete with potassium citrate 10-20 mEq BID
  - Check BMP 2-3 days after starting therapy
  - Check 24 hour urine study 3-4 weeks later
- Uric acid stones
  - Potassium citrate 20 mEq BID
  - Check BMP 2-3 days after starting therapy
  - Check 24 hour urine study 3-4 weeks later
  - +/- patient self-monitoring with pH paper
  - Allopurinol ONLY if urine uric acid is elevated

Dietary Take Home Points

- Fluid intake to maintain urine volume > 2L per day
- Normal calcium intake
  - 1000-1200 mg per day
  - If calcium supplement required - calcium citrate with meals
  - Check 24 hour urine on supplement – may require thiazide
- Strict low salt diet
  - 2300-3300 mg per day
    - 1 tsp = 2300 mg
- Moderate animal protein
  - 6-8 oz meat per day (size of deck of cards)
- Low oxalate
  - Compliance is challenging
  - Appreciate high oxalate foods and maximize fluid intake

Dietary Take Home Points

Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5L daily (Standard: Grade B)

- 1000-1200 mg per day
- If calcium supplement required - calcium citrate with meals

Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit non-dairy animal protein. (Expert Opinion)

- Moderate animal protein

Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid to limit intake of non-dairy animal protein. (Expert Opinion)

- Appreciate high oxalate foods and maximize fluid intake