Influence of Obesity on Urinary Oxalate Excretion

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Disclosures

• None

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Outline

• Epidemiology
• Stone Composition
• 24 hour urine
• Interventions
• UAB/NORC Collaboration
• Conclusions
Epidemiology: Nephrolithiasis

• Nephrolithiasis affects nearly 11% of men and 7% of women in the United States

• National Health and Nutrition Examination Survey (NHANES)
  – NHANES II (1976-1980): 3.8%
  – NHANES (2007-2010): 8.8%

• Men>Women

• Caucasians>African Americans
Epidemiology: Nephrolithiasis

Fig. 2. Prevalence of kidney stones among white men in CPS II, 1982. Estimates are standardized to the age distribution of all CPS II participants.
Epidemiology: Obesity
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1986
(*BMI ≥30, or ~30 lbs overweight for 5’4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1987

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1988

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Obesity Trends* Among U.S. Adults
BRFSS, 1994

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Obesity Trends* Among U.S. Adults

BRFSS, 1995

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Obesity Trends* Among U.S. Adults

BRFSS, 2000

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4’’ person)
Obesity Trends* Among U.S. Adults
BRFSS, 2002

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2004

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005

(*BMI ≥30, or ~ 30 lbs overweight for 5’ 4” person)
Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI $\geq 30$ kg/m$^2$)

1994

2000

2013

Diabetes

1994

2000

2013

No Data <14.0% 14.0%–17.9% 18.0%–21.9% 22.0%–25.9% ≥ 26.0%

No Data <4.3% 4.3%–5.9% 6.0%–7.4% 7.5%–8.9% ≥ 9.0%

Obesity and Stone Disease

- Relative Risk for BMI>30 versus BMI 21-22.9
  - HPFS RR 1.33
  - NHS I RR 1.90
  - NHS II RR 2.09

Waist Circumference and Stone Disease

Body Weight and Stone Disease

Diabetes and Stone Disease

RR with Diabetes

NHS1: 1.38
NHS2: 1.67
HPFS: 1.31

Hypertension and Stone Disease

OR Hypertension in those with Kidney Stone

CARTIA Study: Carotid Artery Atherosclerosis and Stone Disease

- CARTIA observational study
- 5,115 ages 18-30 years
- Follow-up at 2, 5, 7, 10, 15 and 20 years
- Carotid artery IMT (B mode ultrasound)
- 3.9% reported kidney stone at 20 years

Myocardial Infarction and Stone Disease

- Olmsted County Minnesota
- 4564 stone formers matched to 10,860 controls
- Mean follow-up 9 years
- Adjustment for other medical co-morbidities

Metabolic Syndrome

• Definition:
  – Contains at least 3 of the 5 conditions
    • Central (abdominal obesity)
    • Elevated Blood Pressure
    • Elevated Fasting Plasma Glucose
    • High Serum Triglycerides
    • Low high density lipoprotein (HDL) levels
Metabolic Syndrome and Stone Disease

- NHANES III
  - Self reported stone risk 2x higher in those with metabolic syndrome
  - Correlates with number of factors
    - 0 factors: 3.7%
    - 3 factors: 7.5%
    - 5 factors: 9.8%

Outline

- Epidemiology
- **Stone Composition**
- 24 hour urine
- Interventions
- Surgical Issues
- Conclusions
Obesity and Stone Composition

- Most associate uric acid stone with obesity
- Still calcium oxalate in most common

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Urinary Oxalate Excretion and Obesity

- Positive correlation with **body weight**
- Positive correlation with **body surface area**
- Positive correlation with **obesity**
- Positive correlation with **BMI**

Obesity and 24 Hour Urine

- ↓ Citrate Excretion
- ↓ Urine pH
- ↑ Oxalate Excretion
- ↑ Uric acid
- ↑ Calcium Excretion

Obesity and 24 Hour Urine

Calcium (mg per 24 hours):
- BMI < 30: 240
- BMI 25-30: 265
- BMI 35-40: 309
- BMI > 40: 325

Uric acid (mg per 24 hours):
- BMI < 30: 535
- BMI 25-30: 729
- BMI 35-40: 743
- BMI > 40: 789

Oxalate (mg per 24 hours):
- BMI < 30: 28
- BMI 25-30: 31
- BMI 35-40: 40
- BMI > 40: 41

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Interventions: Guideline Statement

• Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 liters daily. (Standard; Evidence strength: Grade B.)

Intervention: Fluid Intake

Relative Risk of Stone

Curhan et al. Annals of Internal Medicine, 126:497, 1997 (NHS I)
Intervention: Guideline Statement

- Clinicians should counsel patients with calcium stones and relatively high urinary calcium excretion to limit sodium intake and consume 1000-1200 mg of dietary calcium per day. (Standard; Evidence Strength: Grade B)
Intervention: Limit Salt, Normal Calcium

- Increased salt, increases urinary calcium and decreases urinary citrate

Sakhaee et al. Journal of Urology, 150:310, 1993

- WHI observational study, sodium intake divided into quintiles

- Risk increased 61% in highest quintile

Intervention: Guideline Statement

• 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)
Vitamin C and Stone Disease

- 1-2 grams per day to CaOx stoneformers
- Increases oxalate excretion 33-61%
- Increases risk of stone formation with >1 gram per day

Intervention: Guideline Statement

• 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).
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P20 Collaboration

- NORC
- Kidney Stone Research Lab
- Courtney Peterson PhD
- Amy Goss PhD
COOKS

• Center for Research on Obesity and Oxalate Kidney Stones
  • https://www.uab.edu/medicine/kidneystone/

• NORC grant support
• Radiology Pilot Project Support
Work at UAB/NORC

589 individuals
Multivariate Analysis: HTN, DM2, BMI, Fatty liver, Race, Sex, Age

- Males excreted more oxalate (Ox) (p=0.0010)
- African Americans had less Ox excretion (p=0.0074)
- Diabetes was associated with more Ox excretion (p<.0001)
- BMI and Ox excretion (p=0.0177)
Sources of Urinary Oxalate

- Diet
- Endogenous synthesis
- Non-enzymatic breakdown of vitamin C
Endogenous Oxalate Synthesis
Animal Studies

• Normal mice were fed a purified diet ultra-low in oxalate and high in fat for 12 weeks
• The control cohort received a normal chow diet
• Ultra low oxalate diet negates the contribution of diet to the urinary oxalate pool thus allowing assessment of endogenous oxalate synthesis
## Animal Studies

<table>
<thead>
<tr>
<th>Diet Induced Obesity</th>
<th>Urinary Oxalate</th>
<th>4 week</th>
<th>10 week</th>
<th>12 week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29.6</td>
<td>36.1</td>
<td>40.3</td>
<td></td>
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<tr>
<td>Urinary Glycolate</td>
<td>39.2</td>
<td>58.4</td>
<td>65.9</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>Urinary Oxalate</td>
<td>29.97</td>
<td>32.55</td>
<td>28.81</td>
</tr>
<tr>
<td>Urinary Glycolate</td>
<td>44.15</td>
<td>42.12</td>
<td>39.19</td>
<td></td>
</tr>
</tbody>
</table>
Animal Studies

24-hr urinary $^{13}$C$_2$-Oxalate (µG)

- Normal fat (17% calories)
- High fat (45% calories)

T-test: P = 0.0485
Wild type (WT) controls (n=6), HFF (n=6) were fed a diet ultra-low in oxalate. Liver tissue was harvested after 12 weeks of feeding. Western blot analysis was performed to assess protein expression of alanine glyoxylate aminotransferase (AGT) and glyoxylate reductase (GR). Mass spectrometry was used for protein measurements in the liver sample.
Animal Studies

WESTERN: Decreases in AGT (p=0.08) expression in HFF
PROTEOMICS: Decreases in AGT (2.2 fold, p=0.004)

WESTERN: Increases in GR (p<0.001)
PROTEOMICS: Increases in GR (1.5 fold, p=0.004).
Human Studies

• 41 healthy subjects, 18-65 years old
• Tightly controlled diet for 3 days
• 16% protein, 30 % fat, 54% carbohydrate
• 30 mg oxalate, 1000 mg calcium
• No vitamin C or calcium supplements
• Collected 24 hour urine samples on days 2 and 3
Methods

• Urinary glycolate and oxalate
• Measured with ion chromatography coupled with mass spectroscopy
A scatter plot illustrates the correlation between 24-hour urinary glycolate (mg) and 24-hour urinary oxalate (mg). The correlation coefficient is $r = 0.31$ and the p-value is $P = 0.049$. The data points are color-coded by gender: black for males and red for females.
36% higher, P=0.011

44% higher, P=0.002
24-hr Urine Oxalate (mg)

Insulin Resistance (µUnits/mL/mg/dL)

P = 0.001
R = 0.49
MRI

• 13 individuals had MRI of abdomen to assess for presence of fatty liver and quantification of pancreatic fat, subcutaneous fat, and visceral fat.
  – % fatty liver was trending with increased urinary oxalate (p=0.146), on unpaired t test fatty liver diagnosis had significantly higher urinary oxalate (p=0.0119)
  – Subcutaneous fat amounts were trending with increased urinary oxalate excretion (p=0.07)
  – % fatty liver was correlated to increased urinary glycolate excretion (p=0.047)
Ascorbic Acid

Change with time of the mole percent enrichment of the plasma Vit C pool with $^{13}\text{C}_6$-Vit C (●) and urinary oxalate pool with $^{13}\text{C}_2$-oxalate (■) following a single oral dose of 50 mg $^{13}\text{C}_6$-Vit C (98%; Cambridge Isotopes). Data expressed as mean ± SD, 2 subjects. The contribution of Vit C breakdown to urinary oxalate, calculated by dividing urinary oxalate mole percent enrichment by the matching plasma Vit C mole percent enrichment, was $45 ± 6\%$. 
Conclusion

• Obesity is associated with increased endogenous oxalate synthesis
• The mechanisms for this increased oxalate production need to be defined
• Increased glycolate production or glycolate transport may play a role
• Insulin Resistance may play a role
• Ascorbic Acid may be a source of oxalate
Future Studies

- Carbon-13 labelled precursors (C13 Glycolate and AA)
- MRI with fat distributions
- Animal work to understand enzymatic changes
- Weight loss interventions
- Various diets
- Insulin Resistance, Glucose Tolerance
Dean Assimos MD

- Chair of Urology Department
- Stone Guru
- Mentor

- Will now discuss: Uric Acid
Thanks