Uric Acid and Cardiovascular Risk: From Bench to Bedside

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Topics for Discussion

• History and basic biochemistry
• Epidemiology and controversy: A role for uric acid in hypertension, CVD and CKD?
• Animal model data: A mechanism by which uric acid causes hypertension and vascular injury
• Clinical trial data: Lowering uric acid can lowers BP in young subjects
• Clinical recommendations?

Uric Acid and Hypertension

"People who are subject to this high blood pressure diathesis frequently belong to gouty families, or have themselves suffered from the symptoms of this disease"

Frederick Mahomed.
Lancet i:400, 1879

Meet Uric Acid

CS H4 N4 O3
Uric Acid: A Product of Purine Metabolism

- Purines
- Xanthine oxidase
- Xanthine
- Xanthine oxidase
- Uric Acid
- Urate oxidase (Uricase)
- Allantoin
- Other mammals

Man and Great Apes

Causes of Hyperuricemia

- Exposures
  - Obesity
  - High protein diet
  - High fructose
  - Alcohol consumption
  - Heavy metals
- Genetic Conditions
  - Urate Transporters
  - JFHN
  - Lesch Nyhan
  - *? Purine recovery

- Mechanisms
  - Excess intake
  - Decreased GFR
  - Transporter/Channel defects
  - Tumor or other cell lysis
  - *? Defects in purine recovery pathways
  - Excess requirements for nitrogen disposal

Fructose and Uric Acid

Fructose → ATP depletion
ATP → ADP → AMP → Uric acid

Epidemiology of Uric Acid and Cardiovascular Disease

Cardiovascular Death or Major Events in Elderly Patients (SHEP Trial)

Age-Adjusted Cardiovascular Mortality Rates by Quartile of Serum Uric Acid Level

NHANES

Hyperuricemia Predicts Cardiovascular Events: 19 Studies on CV or all cause mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th>Age</th>
<th>FU</th>
<th>OR</th>
<th>Adj.</th>
<th>Independent</th>
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<td>Ahsan</td>
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<td>De Zeeuw</td>
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<td>2</td>
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<td>Simon</td>
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</table>

Hyperuricemia Predicts Incident Hypertension: 11 Longitudinal Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Yr publ</th>
<th>Popul.</th>
<th>Age</th>
<th>FU</th>
<th>OR</th>
<th>Adj.</th>
<th>CKD</th>
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<tr>
<td>Israeli Heart Study</td>
<td>1972</td>
<td>6500</td>
<td>18-31</td>
<td>15</td>
<td>1.62</td>
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<tr>
<td>Kaiser Permanente</td>
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<tr>
<td>Olivetti Heart Study</td>
<td>1994</td>
<td>619</td>
<td>49</td>
<td>12</td>
<td>1.23</td>
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<td>Japan Men’s Health</td>
<td>2003</td>
<td>4489</td>
<td>45</td>
<td>23</td>
<td>1.93</td>
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<td>Framingham Study</td>
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<td>3329</td>
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<td>4</td>
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<td>Bogalusa Study</td>
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<td>5-17</td>
<td>12</td>
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<td>Beaver Dam, Wisc</td>
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<td>48-84</td>
<td>10</td>
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<td>Normative Aging</td>
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<td>46</td>
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<td>ARIC (Ath. Risk Com)</td>
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<td>7</td>
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<td>Health Prof. F/U</td>
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<td>61</td>
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<td>MR FIT</td>
<td>2007</td>
<td>3073</td>
<td>35-57</td>
<td>6yr</td>
<td>1.81</td>
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Why Is This Controversial?

- Despite consistent correlation, some reports found uric acid was not an independent risk factor
- There was no mechanistic link between uric acid and hypertension or CV disease
- By the late 1980s uric acid was removed from most laboratory panels (SMAC 20, etc)
- Late 1990s: uric acid was a surrogate for renal function which was definitely an important risk factor.

Uric acid and CKD

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Year</th>
<th>Population</th>
<th>Finding</th>
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</thead>
<tbody>
<tr>
<td>Jaski</td>
<td>2001</td>
<td>6403, Okinawa Health</td>
<td>2x risk men, 10x women</td>
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<tr>
<td>Chonchol</td>
<td>2007</td>
<td>5000 CV Health study</td>
<td>Assess prevalent CKD</td>
</tr>
<tr>
<td>Chowney</td>
<td>2008</td>
<td>21,457 Vienna Health Screen</td>
<td>1.74 in men, 2.2x in women</td>
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<tr>
<td>Doore</td>
<td>2008</td>
<td>227-HMDD</td>
<td>Predicted progression</td>
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<tr>
<td>Weiner</td>
<td>2008</td>
<td>13,338 ARIC</td>
<td>Linear association uric acid, CKD risk</td>
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<td>Borges</td>
<td>2009</td>
<td>365, Women’s Health</td>
<td>1.65 risk in women</td>
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<tr>
<td>Chen, N</td>
<td>2009</td>
<td>2396, Zhejiang</td>
<td>Linear correlation</td>
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<tr>
<td>Chen, Y</td>
<td>2009</td>
<td>5723, Taipei Univ</td>
<td>CKD risk in elderly</td>
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<tr>
<td>Mats</td>
<td>2009</td>
<td>177,770 USRDS</td>
<td>Highest quartile 3x risk of ESRD</td>
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<tr>
<td>Medrano</td>
<td>2009</td>
<td>940, National CV Institute, Mexico</td>
<td>No increased progression risk</td>
</tr>
<tr>
<td>Seo</td>
<td>2009</td>
<td>28,745 Chung-Gang Univ</td>
<td>Only weak assoc uric acid, CKD</td>
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</tbody>
</table>

Epidemiology of Uric Acid: Jan 1 –July 10, 2009

- 54 new publications
- 20 confirming association of uric acid and CV mortality risk
- 18 confirming association of uric acid and hypertension in various population
- 6 uric acid predicts CKD
- 4 uric acid and risk of incident type 2 diabetes
- 3 uric acid predicts hypertensive target organ damage
- 2 Uric acid and hypertension in renal transplant patients
- 1 uric acid predicts diabetic nephropathy

Experimental Hyperuricemia in the Rat
A Model of Mild Hyperuricemia

Uricase inhibitor

Oxonic acid (OA)

Normal Rat
Uric Acid
(0.5-1.4 mg/dl)

Hyperuricemic Rat
Uric Acid
(2.7-4.0 mg/dl)

Hyperuricemia Induces Hypertension

Mazzali et al., Hypertension 2001; 38:1101-6

Hyperuricemia Increases Renin Expression

Mazzali et al, Hypertension 38:1101-1106, 2001

Hyperuricemia Inhibits Nitric Oxide Production in Rats

Khosla et al., Kid. Int. 2005, 67:1739

Hyperuricemia Induces Salt-Sensitivity

Watanabe S et al., Hypertension 2002; 40:355-360

Hyperuricemia Induces Preglomerular Vascular Disease

Mazzali et al, AJP Renal Physiol 282:F991, 2002
**Uric Acid Causes Arteriolosclerosis in a BP Independent Fashion**

Mazzalli et al, AJP Renal Physiol 282:F991, 2002

**Uric Acid Activates Vascular Smooth Muscle Cells**

**Model of Hyperuricemic Hypertension**

**Hyperuricemia in Pediatric Patients**

**Why Study Kids?**

- Fewer chronic diseases that confound assessment
- Shorter duration of disease allows separation of etiology from end organ damage
- If hypertension is a two step disease, newly diagnosed adults may already be in second phase

**Definition of Hypertension**

  - Stratified by gender, age and height
  - Pre-Hypertension: 85-95%ile
  - Special Populations: >90%ile
  - Stage I Hypertension: >95%-ile
  - Stage II Hypertension: >99%ile+5

*On 3 Consecutive, encounters over >2wks*
### Blood Pressure Tables

**Systolic Blood Pressure - 11 year old Boy**

<table>
<thead>
<tr>
<th>Height Percentile</th>
<th>5th</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>50th</td>
<td>99</td>
<td>100</td>
<td>102</td>
<td>104</td>
<td>105</td>
<td>107</td>
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<td>90th</td>
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<td>117</td>
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<td>120</td>
<td>121</td>
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<td>95th</td>
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<td>99th</td>
<td>124</td>
<td>125</td>
<td>127</td>
<td>129</td>
<td>130</td>
<td>132</td>
<td>132</td>
</tr>
</tbody>
</table>

### Evaluation of Children with Hypertension

- **H & P**
- **ABPM**
- **Laboratory Screening** (CBC, Chemistries, Lipids, renin profile, uric acid)
- **Renal US**
- **Echocardiogram**
- ± renal perfusion scan, renal artery imaging

### Serum Uric Acid in Children with Hypertension

- **Essential Hypertension**
  - Mean = 6.7
- **Secondary Hypertension**
  - Mean = 4.3
- **White Coat Hypertension**
  - Mean = 3.6
- **Controls**
  - Mean = 3.6

*Feig and Johnson, Hypertension, 2003;42:247-52*

### Serum Uric Acid and BP Correlate Closely

*Feig and Johnson, Hypertension, 2003;42:247-52*

### Patient Population

- **Age**: 15.1 ± 2.1 yrs
- **% Male**: 60%
- **Height**: 170 ± 8.7 cm
- **Weight**: 97 ± 23 kg
- **BMI**: 33 ± 6.5 kg/m²
- **Race**: W46% / H23% / AA31%
- **Uric Acid**: 6.9 ± 1.2 mg/dL (plac 6.4 ± 1.6 / Allo 4.2 ± 1.3)
**Effect of Allopurinol on Blood Pressure**

**Exploratory Endpoints**

<table>
<thead>
<tr>
<th></th>
<th>Pre-Rx</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beat/min)</td>
<td>72±13</td>
<td>74±15</td>
<td>75±12</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>6.4±1.6</td>
<td>6.2±1.8</td>
<td>6.6±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>SVR index (mmHg/dynes/cm²/m²)</td>
<td>2478±1550</td>
<td>2473±750</td>
<td>2136±396</td>
<td>0.01</td>
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<tr>
<td>Renin (ng/ml/hr)</td>
<td>1.9±1.3</td>
<td>2.1±1.6</td>
<td>1.4±1.2</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Alternative Explanation?**

- George et al. Circulation 2006, 114: 2508
- Assessed endothelial function by vasodilatory response to ACh vs. NPr in elderly CHF patients
- Allopurinol vs. placebo OR Probenecid vs. placebo
- Allopurinol restored NO mediated dilation in dose responsive manner; Probenecid did not
- Conclusion: Xanthine oxidase mediated superoxide is the cause of endothelial dysfunction, not uric acid.

**PHOA**

Prevention of Hypertension in Obese Adolescents

- Randomized placebo controlled trial of allopurinol vs. probenicid vs. placebo
- Obese adolescents with pre-hypertension
-Endpoints: SVR, RAS and inflammatory status
- Completed

**PHOA Trial**

Prevention of Hypertension in Obese Adolescents

- 60 Adolescents
  - BMI >30kg/m²
  - Pre-hypertension
  - Urac acid >5mg/dL
  - No current meds
  - Never Rx’d for HTN

- Screen and Randomize
- 20 Adolescents, 2 mo Placebo
  - 1 mo f/u
- 20 Adolescents, 2 mo Probenecid
  - 1 mo f/u
- 20 Adolescents, 2 mo Allopurinol
  - 1 mo f/u
**Allopurinol and Probenecid**

lower uric acid and BP

<table>
<thead>
<tr>
<th>Rx'd Uric Acid</th>
<th>Placebo</th>
<th>Probenecid</th>
<th>Allopurinol</th>
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</thead>
<tbody>
<tr>
<td>Wt (Kg)</td>
<td>5.9±2.4</td>
<td>4.3±1.8</td>
<td>3.4±1.4</td>
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<tr>
<td>Δ Wt (Kg)</td>
<td>+3.4±2.1</td>
<td>+1.6±2.0</td>
<td>-0.4±1.8</td>
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<tr>
<td>post SBP</td>
<td>128±2.7 (1.4)</td>
<td>125±3.4 (1.3)</td>
<td>117±5.3 (1.1)</td>
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<tr>
<td>post DBP</td>
<td>74±6.9 (-1.6)</td>
<td>61±3.1 (-1.0)</td>
<td>69±5.6 (-0.9)</td>
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<tr>
<td>post 24hr SBP</td>
<td>122±4.1 (-2)</td>
<td>116±11.7 (1.4)</td>
<td>115±10 (-6.8)</td>
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<tr>
<td>post 24hr DBP</td>
<td>77±3.9 (+1)</td>
<td>60±3.1 (-10.7)</td>
<td>63±4.4 (-0.9)</td>
</tr>
<tr>
<td>Urine microab</td>
<td>4.0±3.2</td>
<td>0.7±9.19</td>
<td>0.6±0.22</td>
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</table>

**Clinical Trials on CKD and uric acid**

- 54 patients with mean serum uric acid 9.8mg/dL and CKD 3-4 were treated allopurinol and compared to historical controls. Possibly slower progression to ESRD
  
  *Sui, AJKD 2006, 47:51*

- 59 patients CKD 1 randomized to allopurinol or placebo. Allopurinol patients had mean increase in GFR of 12ml/min
  
  *Kanbay, Int Urol Nephrol 2007, 39:1227*

**Summary of Human Data**

- Uric acid correlates with the development of essential hypertension in children
- Allopurinol lowers BP in children with newly diagnosed essential hypertension and serum uric acid >6.0mg/dl
- Probenecid also lowers BP indicating that uric acid is the relevant molecule
- Exploratory endpoints suggest allopurinol lowers renin and SVR
- Preliminary results suggest hypouricemic therapy may improve GFR.

**RAPHY Trial:**

Reduction of uric Acid to Prevent HYpertension

- 520 subjects 13-25yo
  - Prehypertension and uric acid >5.5mg/dL
  - Randomize to placebo, DASH diet, probenecid, allopurinol
  - 12 mo treatment, 6-12 mo follow up
  - Primary endpoint change in DBP over time
  - Numerous mechanistic secondary endpoints
  - Enrollment: August 2010

**Pathogenesis of Essential Hypertension**

- Sympathetic Nervous System Overactivity
  - Increased renin, Angiotensin
  - Toxins (lead, cyclosporine)
  - Early Vasoconstriction
  - Interstitial Inflammation
  - Arteriolar Disease
  - Dec. pressure natriuresis
  - Sodium retention
  - Hypertension
  - Decreased Nephron Number
  - Uric Acid
  - Endothelial Injury

**NAFLD and Uric Acid**

- Children presenting to Baylor Pediatric Bariatric Surgery Program
- Linear and multiple regression of factors associated with NAFLD
- Uric acid closest correlation with grade of NAFLD ($r=0.783$)
  - equal to elevated transaminases ($r=0.791$),
  - better correlation than BMI ($r=0.233$),
  - Insulin Resistance ($r=0.446$),
  - Triglycerides ($r=0.136$)

*Fuller et al., in press 2009*
Obesity and Hyperuricemia

Risk of Obesity Related Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>BMI &lt;25</th>
<th>25-30</th>
<th>30-35</th>
<th>&gt;35</th>
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<td>1.00</td>
<td>1.39</td>
<td>1.86</td>
<td>1.67</td>
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<tr>
<td>Stroke</td>
<td>1.00</td>
<td>1.53</td>
<td>1.59</td>
<td>1.75</td>
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<tr>
<td>T2-DM</td>
<td>1.00</td>
<td>2.42</td>
<td>3.35</td>
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<td>Htn</td>
<td>1.00</td>
<td>1.92</td>
<td>2.82</td>
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</table>

Increasing Prevalence of Childhood Obesity

<table>
<thead>
<tr>
<th>Year</th>
<th>Ages 6-11 yr</th>
<th>Ages 12-18 yr</th>
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<tr>
<td>1971-1974</td>
<td>4.3% / 3.6%</td>
<td>6.1% / 6.2%</td>
</tr>
<tr>
<td>1988-1994</td>
<td>11.6% / 11%</td>
<td>11.3% / 9.7%</td>
</tr>
<tr>
<td>1999-2000</td>
<td>16% / 14.5%</td>
<td>15.5% / 15.5%</td>
</tr>
<tr>
<td>2005</td>
<td>18.7% / 18%</td>
<td>21.1% / 19.2%</td>
</tr>
</tbody>
</table>

Obesity and Uric Acid

- Linear correlation between BMI and serum uric acid in Asians, Hispanics, African Americans
- Rise in BMI inversely correlated with renal urate clearance
- Inverse correlation between serum uric acid and adiponectin
- Activation of VSM proliferation and endothelium associated inflammation may contribute to target organ damage

Sugar and Obesity

Fructose and Uric Acid

Fructose loading increases BP and Triglycerides

Time in hrs

Change in Triglycerides (mg/dL)


Fructose and Uric Acid

• Animal Data
  • High Fructose diet cause increased uric acid, triglycerides and BP in rats
  • High fructose diet causes increase uric acid, BP and insulin resistance that is ameliorated by xanthine oxidase inhibition but not HCTZ or CCB

• Human Data
  • High fructose diet is associated with increased adiposity, dyslipidemia and insulin resistance
  • 10wk trial of high fructose drink added to every meal increased uric acid, BP, and ApoB
  • NHANES III, recall history of sweetened beverage intake correlates with serum uric acid and elevated blood pressure
    Nguyen, J. Pediatr 2009 154: 807

The case for uric acid

• Epidemiology: Increased uric acid predicts hypertension, CKD and CV morbidity
• Experimental Animals: increased uric acid causes hypertension through a two step process, the second of which is irreversible
• Clinical trial: lowering uric acid improves blood pressure in adolescents. Response in CKD unproven but suggestive.

Clinical Considerations

• Standard indications for urate lowering
  • Acute symptomatic gout
  • Prophylaxis for recurrent or severe gout
  • Treatment or prophylaxis for tumor lysis syndrome or its risk
• Available therapies
  • Xanthine oxidase inhibitors (allopurinol, febuxostat)
  • Uricosurics (probenecid, others in development)
  • Mild urocosurics (losartan, statins, some abx)
  • Stop drugs that increase uric acid (thiazides)
Risks of therapy

- GI upset
- Increased transaminases
- Drug interactions (especially allopurinol, azathioprine)
- Allopurinol hypersensitivity syndrome
- Uric acid stones with uricosurics

Non-standard hyperuricemia

- Adults with hypertension and hyperuricemia
  - Uric acid reduction is theoretically helpful but not proven. Conventional antihypertensive treatment is proven to reduce endpoints
- Adults with CKD
  - No proven efficacy but fewer proven options except for diabetic nephropathy

Can hypertension and CKD progression be prevented?

- If animal models can be trusted, two phases of hypertension development
- Long term prevention may be possible with early intervention
- Early use of diuretics could, theoretically, be counterproductive
- Much more evidence is needed to if changing current consensus recommendations is to be considered

Uric Acid - the Scourge of Humanity?

Haig, Alexander, 1892
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