The significance of uric acid in hypertensive treatment

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Uric Acid

Dietary purines, fructose, alcohol

Liver

Intestine

De novo purine synthesis
Purine catabolism

XO

Urate in blood
3-10 mg/dl
(180-600 μM)

Muscle
(strenuous exercise)

Cellular degradation:
leukemia, lymphomas,
chemotherapy

XO in other organs: lung, brain, etc.

Kidney

Filtration

Reabsorption

Secretion

Postsecretory reabsorption

Uric acid
“Uric acid was first associated with primary hypertension”

Mahomed FA. Med Chir Trans, 1874
Mahomed FA. Lancet, 1879
High-tension pulse of a uric acid headache

Haig A, 1892
Urodonal

A treatment for lowering serum UA, treatment for arteriosclerosis and obesity

From French newspaper advertisement, Dec. 20th, 1919
The Role of Uric Acid in HTN: Chicken or Egg?
Uric acid is commonly elevated in patients with hypertension
A strong relationship between UA and HTN:

- **25-50%** of untreated primary hypertension
- **75%** of pts. if the hypertension was malignant or if there was coexistent renal disease

**Cannon PJ, et al. NEJM, 1966**
• Frequency of HTN in adult pts. with asymptomatic hyperuricemia is about 50%.

• About 60% - 65% of pts. with gout have HTN.

• Western diet with increased frequency of HTN.

Johnson RJ, et al. Semin Nephrol 2005
Uric acid elevation is increased secondary to hypertension
Causes of Hyperuricemia in HTN

Possible mechanisms

1) Increased net reabsorption of UA
   - Diuretics use
   - Insulin resistance
   - Reduced renal blood flow

2) Decreased renal excretion
   - Decreased renal excretion of UA d/t renal dysfunction
   - Lactate competes with UA excretion

3) Increased production
   - Increased activity of XO (endothelium)
   - Increased conversion of XDH to XO
   - Increased XO substrate resulting from increased adenosine and hypoxanthine
Pathophysiologival Role of XO pathways in HTN

Adenosine
   ↓
Inosine
   ↓
Hypoxanthine
   ↓
Xanthine
   ↓
Uric acid
   ↓

O$_2^-$
   +
Allopurinol
   ↓
Oxypurinol
   +

Xanthine oxidase

Urate Oxidase

Excretion:

Allantoin

Renal (2/3)
Gastrointestinal (1/3)

Elevated uric acid predicts the development of hypertension
Table 3. Hyperuricemia and the Development of Hypertension.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Relative Risk of Hypertension</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaiser Permanente, 1990</td>
<td>2062 adults</td>
<td>2.1 times greater at 6 yr (high vs. low quintile)</td>
<td>1.20–3.98</td>
</tr>
<tr>
<td>University of Utah, 1991</td>
<td>1482 adults</td>
<td>1.44 times greater per SD increment at 7 yr</td>
<td>1.03–2.01</td>
</tr>
<tr>
<td>Olivetti Heart, 1994</td>
<td>619 men</td>
<td>1.23 times greater per 1 mg/dl increase at 12 yr</td>
<td>1.07–1.39</td>
</tr>
<tr>
<td>CARDIA, 1999</td>
<td>5115 men</td>
<td>1.21 times greater per SD increment at 10 yr</td>
<td>1.03–1.41</td>
</tr>
<tr>
<td>Osaka Health Survey, 2001</td>
<td>6356 men</td>
<td>2 times greater at 10 yr (high vs. low quintile)</td>
<td>1.56–2.60</td>
</tr>
<tr>
<td>Hawaii–Los Angeles–Hiroshima, 2001</td>
<td>140 men</td>
<td>2.0 times greater at 15 yr (high vs. low quartile)</td>
<td>1.02–3.9</td>
</tr>
<tr>
<td>Osaka Factory, 2003</td>
<td>433 men</td>
<td>1.0 mg/dl, increased 27 mm Hg SBP at 5 yr</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Osaka Health Survey, 2003</td>
<td>2310 men</td>
<td>1.13 times greater per SD increment at 6 yr</td>
<td>1.06–1.21</td>
</tr>
<tr>
<td>Okinawa, 2004</td>
<td>4489 adults</td>
<td>1.46 times greater for men (uric acid ≥7 mg/dl) and 1.94 for women (uric acid ≥6 mg/dl) at 13 yr</td>
<td>1.09–2.03, 1.05–3.57</td>
</tr>
<tr>
<td>Bogalusa Heart, 2005</td>
<td>679 children</td>
<td>Increased risk for diastolic hypertension at 11 yr</td>
<td>Not calculated</td>
</tr>
<tr>
<td>Framingham Heart, 2005</td>
<td>3329 adults</td>
<td>1.17 times greater per SD increment at 4 yr</td>
<td>1.02–1.33</td>
</tr>
<tr>
<td>Normative Aging, 2006</td>
<td>2062 men</td>
<td>125 times greater at 21 yr (uric acid ≥6.5 mg/dl)</td>
<td>1.08–1.34</td>
</tr>
<tr>
<td>ARIC, 2006</td>
<td>9104 adults</td>
<td>1.1 times greater per SD increment at 9 yr</td>
<td>1.02–1.14</td>
</tr>
<tr>
<td>Beaver Dam Health Survey, 2006</td>
<td>2520 adults</td>
<td>1.65 times greater at 10 yr (high vs. low quintile)</td>
<td>1.41–1.93</td>
</tr>
<tr>
<td>Health Professionals’ Follow-up, 2006</td>
<td>750 men</td>
<td>1.02 times greater per SD increment at 8 yr</td>
<td>0.92–1.13</td>
</tr>
<tr>
<td>MRFIT, 2007</td>
<td>3073 men</td>
<td>1.1 times greater per SD increment at 6 yr</td>
<td>1.02–1.19</td>
</tr>
</tbody>
</table>

Feig D et al, NEJM, 2008
Prevalence of Hyperuricemia

- 2~35% in general population
- 25~50% of untreated primary hypertension
- 50% of hypertension on diuretics
- 70~100% of malignant hypertension
- ~ 50% in CKD at the onset of renal replacement therapy
According to Meta-analysis (N=55,607)

Hyperuricemia

- Increase of 1 mg/dl of UA → risk of hypertension 13%
  - Primary > Secondary HTN
  - Shorter duration of HTN > Longer duration
  - Younger > Older
  - Female > Male

Risk of hypertension: 42%↑

UA and Blood Pressure in Japanese Men

Study Subjects

Neither anti-HTN or UA lowering drugs

Subjects with anti-HTN but not UA lowering drugs

Kansui Y. et al. Circ J 2011;75:2827-2832
UA may play a role in the development of TOD in hypertension
**Relationship between UA and PWV, IMT, albuminuria**


PWV

Table 3
Independent determinants of logarithm of urinary albumin excretion

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diabetes</td>
<td>.253</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>.166</td>
<td>.0034</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>.125</td>
<td>.0472</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>.275</td>
<td>.0013</td>
</tr>
<tr>
<td>Uric acid</td>
<td>.281</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

$R^2 = 0.252$ ($P < .0001$).


IMT

Kawamoto R, et al. Internal Medicine, 2006

# Relationship between UA and LVH

**Table 2. Association Between UA Tertile and Prevalence of LVH by Multivariate Logistic Regression Analysis (n=3,305)**

<table>
<thead>
<tr>
<th>UA tertile</th>
<th>No. of LVH (%)</th>
<th>Crude</th>
<th>Model 1*</th>
<th>Model 2†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>155/1,109 (14.0)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Middle</td>
<td>188/1,123 (16.7)</td>
<td>1.24 (0.98–1.56)</td>
<td>1.29 (1.02–1.64)</td>
<td>1.28 (1.01–1.63)</td>
</tr>
<tr>
<td>Highest</td>
<td>211/1,073 (19.7)</td>
<td>1.51 (1.20–1.89)</td>
<td>&lt;0.001</td>
<td>1.61 (1.26–2.06)</td>
</tr>
</tbody>
</table>

*Adjusted for institute, age, BMI, HTN and log-transformed Creat.
†Adjusted for institute, age, BMI, HTN, DM, HL and log-transformed Creat.
OR, odds ratio. Other abbreviations see in Table 1.

**Table 3. Association Between UA Tertile and the Prevalence of LVH in the Sample Stratified by Presence of HTN (n=3,305)**

<table>
<thead>
<tr>
<th>UA tertile</th>
<th>No. of LVH (%)</th>
<th>Normotensive group (n=2,652)</th>
<th>Hypertensive group (n=653)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>99/845 (11.7)</td>
<td>1 (reference)</td>
<td>54/212 (25.5)</td>
</tr>
<tr>
<td>Middle</td>
<td>134/899 (14.9)</td>
<td>1.35 (1.01–1.80)</td>
<td>54/226 (23.9)</td>
</tr>
<tr>
<td>Highest</td>
<td>135/908 (14.9)</td>
<td>1.43 (1.06–1.92)</td>
<td>78/215 (36.3)</td>
</tr>
</tbody>
</table>

Normotensive defined as SBP<140 mmHg and DBP<90 mmHg; Hypertensive defined as SBP≥140 mmHg and/or DBP≥90 mmHg.
*Adjusted for institute, age, BMI, SBP, DM, HL and log-transformed Creat.
Abbreviations see in Tables 1,2.

*Tsioufis C. et al. J Human Hypertension, 2005*
Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

Yui-Pong Siu, MRCP, Kay-Tai Leung, MRCP, Matthew Ka-Hang Tong, MRCP, and Tze-Hoi Kwan, FRCP

Albuminuria

UA is also related with CV diseases in hypertensive patients
Hyperuricemia predicts CV events: Studies of the Hypertensive Population

<table>
<thead>
<tr>
<th>Study</th>
<th>Length of Follow-Up, y</th>
<th>Univariate Correlation with Events</th>
<th>Independent Predictor in Multivariate Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension Detection Follow-Up Program Cooperative Research Group</td>
<td>5</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1985</td>
<td>5</td>
<td>Yes</td>
<td>Only women</td>
</tr>
<tr>
<td>1987</td>
<td>5†</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Work site</td>
<td>6.6</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>1999</td>
<td>6.6</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>PIUMA (Progetto Ipertensione Umbria Monitoraggio Ambulatoriale)</td>
<td>4</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>4</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>European Working Party on High BP in the Elderly</td>
<td>3</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td>3</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>SHEP (Systolic Hypertension in the Elderly Program)*</td>
<td>5</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>5</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Syst-China*</td>
<td>3</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>3</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Syst-Eur*</td>
<td>2</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with isolated systolic hypertension; †subanalysis of patients on thiazides.

Johnson RJ. et al. Hypertension 2003;41:1183-1190
Serum Uric Acid and Risk for Cardiovascular Disease and Death:
The Framingham Heart Study

Bruce F. Cuseto, MD; Martin G. Larson, ScD; William B. Kannen, MD; and Daniel Levy, MD

Background: Hyperuricemia is associated with risk for cardiovascular disease and death. However, the role of uric acid independent of established risk factors is uncertain.

Objective: To examine the relation of serum uric acid level to incident coronary heart disease, death from cardiovascular disease, and death from all causes.

Design: Community-based, prospective observational study.

Setting: Framingham, Massachusetts.

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (1). Several prospective studies have shown an association between baseline hyperuricemia and incident coronary heart disease, cardiovascular disease, and death (2–10). Despite the strength of these associations, uric acid has not been established as a causal risk factor for cardiovascular disease. Instead, uric acid seems inextricably linked to hypertension, dyslipidemia, and disordered glucose metabolism, and 1450 deaths from all causes occurred. In men, after adjustment for age, elevated serum uric acid level was associated with increased risk for an adverse outcome. In women, after adjustment for age, uric acid level was predictive of coronary heart disease (P = 0.002), death from cardiovascular disease (P = 0.009), and death from all causes (P = 0.03). After additional adjustment for cardiovascular disease risk factors, uric acid level was no longer associated with coronary heart disease, death from cardiovascular disease, or death from all causes. In a stepwise Cox model, diuretic use was identified as the covariate responsible for rendering serum uric acid a statistically nonsignificant predictor of outcomes.

Conclusions: These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

UA does not have causal role in the development of CHD, CV mortality and all-cause mortality
Experimental studies suggest a causal role for uric acid in hypertension
Animal Model of Mild Hyperuricemia

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

Hyperuricemic Rat
Uric Acid (1.7-3.0 mg/dl)

Uricase inhibitor
Oxonic acid (OA)

Experimental studies
- Renal hemodynamics

*Hyperuricemic rats*

- A marked increase in glomerular hydrostatic pressure
- Increase in renal afferent arteriolar resistance
- Decrease in renal blood flow

- Associated with increased oxidative stress, endothelial dysfunction and RAS activation
Renal arteriolar microvascular disease, mild interstitial inflammation

Effect of UA on VSMC proliferation


*P>0.05, **P<0.01 UA vs UA+Losartan (0.1, 0.5 µM)
Proposed mechanism by which UA may cause HTN

Hyperuricemia

- Induction of oxidative stress
- Activation of the RAS
- Inhibition of NO via oxidants, arginase, and direct inactivation to aminouracil

Vascular smooth muscle cell proliferation
Endothelial cell dysfunction
Inflammation

Development of renal arteriolar disease
Interstitial macrophage and T-cell infiltration

Renal vasoconstriction and ischemia

Early: minimal microvascular disease
Parallel shift
Salt-resistant hypertension

Late: significant microvascular disease
Right shift
Salt-sensitive hypertension

Uric acid may also have a role in:
- Metabolic syndrome
- Obesity
- Chronic kidney disease
Interventional studies have supported a role for UA in hypertension
Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions

This was one of the first articles to show the potential effect of lowering UA on blood pressure

<table>
<thead>
<tr>
<th></th>
<th>Allopurinol group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After 3 months</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>8.0 ± 0.76</td>
<td>5.5 ± 1.2*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.24 ± 0.36</td>
<td>1.14 ± 0.32*</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>79.2 ± 31.9</td>
<td>92.9 ± 36.8*</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.8 ± 1.4</td>
<td>2.5 ± 1.3*</td>
</tr>
<tr>
<td>Urine protein (mg/day)</td>
<td>134.5 ± 132.0</td>
<td>131.5 ± 108.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>135.4 ± 4.6</td>
<td>131.5 ± 4.1*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.2 ± 6.2</td>
<td>78.3 ± 3.1*</td>
</tr>
</tbody>
</table>

*P < 0.05
Effect of Allopurinol on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension
A Randomized Trial

This was the first placebo-controlled trial to show an effect of lowering UA on blood pressure

Figure 2. Blood Pressure Response of Adolescents to Allopurinol and Placebo

**EFFECT OF ALLOPURINOL IN CHRONIC KIDNEY DISEASE (CKD) PROGRESSION AND CARDIOVASCULAR RISK**

- 113 CKD patients with eGFR<60 ml/min
- Allopurinol 100 mg/day vs. placebo
- 12 months

<table>
<thead>
<tr>
<th></th>
<th>Uric acid (mg/dl)</th>
<th>hsPCR (mg/l)</th>
<th>Cystatin (mg/l)</th>
<th>Albuminuria (mg/day)</th>
<th>Fibrinogen (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Control group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>7.3±1.6</td>
<td>3.4(5.2)</td>
<td>2.0±0.7</td>
<td>32(383)</td>
<td>384±104</td>
</tr>
<tr>
<td>6 months</td>
<td>7.0±1.6</td>
<td>3.0(7.6)</td>
<td>2.0±0.8</td>
<td>43(417)</td>
<td>373±112</td>
</tr>
<tr>
<td>12 months</td>
<td>7.4±2.0</td>
<td>3.2(10.8)</td>
<td>1.9±1.0</td>
<td>51(296)</td>
<td>402±98</td>
</tr>
<tr>
<td><strong>Allopurinol group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>7.8±2.1</td>
<td>4.4(4.5)</td>
<td>1.9±0.5</td>
<td>36(388)</td>
<td>381±78</td>
</tr>
<tr>
<td>6 months</td>
<td>6.2±1.5</td>
<td>3.0(4.0)</td>
<td>1.8±0.6</td>
<td>15(103)</td>
<td>367±58</td>
</tr>
<tr>
<td>12 months</td>
<td>6.0±1.8</td>
<td>3.0(2.5)</td>
<td>1.4±0.4</td>
<td>16(166)</td>
<td>369±49</td>
</tr>
</tbody>
</table>

* p=0.016 between groups and time periods (two-way ANOVA)
** p=0.018 between groups and time periods (two-way ANOVA)

Goicoechea M et al, CJASN
Uricosuric Action of Losartan via the Inhibition of Urate Transporter 1 (URAT1) in Hypertensive Patients

Toshihiro Hamada¹, Kimiyoshi Ichida², Makoto Hosoyamada³, Einosuke Mizuta¹, Kiyotaka Yanagihara¹, Kazuhiko Sonoyama¹, Shinobu Sugihara¹, Osamu Igawa¹, Tatsuo Hosoya⁴, Akira Ohtahara⁵, Chiaki Shigamasa¹, Yasutaka Yamamoto⁶, Haruaki Ninomiya⁷ and Ichiro Hisatome⁶

BACKGROUND
The angiotensin receptor blocker losartan inhibited urate transporter 1 (URAT1) according to in vitro experiments. However, it is still unknown whether the inhibitory effect of losartan on URAT1 contributes to its uricosuric action in humans.

METHODS
Thirty-two patients with hypertension and nine patients with idiopathic renal hypouricemia (five with and four without hypertension) were enrolled for this study. Hypertensive patients were prescribed oral losartan (50 mg/day, n = 16) or candesartan (8 mg/day, n = 16). Before and after 1-month treatment, the serum concentration of urate (Sur) and creatinine (Scr), and the clearance value of urate (Cur) and creatinine (Ccr) were determined. Clearance studies using the URAT1 inhibitor benzbromarone (100 mg/day) or losartan (50 mg/day) loading test were also performed in these patients.

RESULTS
Blood pressure (BP) significantly decreased in the patients treated with either losartan or candesartan. Losartan significantly reduced Sur, which was associated with a concomitant increase in the Cur/Ccr ratio, whereas candesartan did not alter these parameters. In hypertensive patients with loss-of-function mutation of URAT1, losartan did not alter either Sur or Cur/Ccr, nor did benzbromarone. The lack of effect of URAT1 inhibitors on renal excretion of urate was independent of the renal function of hypouricemic patients. On the other hand, both losartan and benzbromarone increased Cur/Ccr ratio in hypertensive patients harboring the wild URAT1 gene, regardless of the presence of hypouricemia.

CONCLUSIONS
These findings suggested that losartan inhibited URAT1 and thereby it lowered Sur levels in hypertensive patients.

Role of Uric Acid in Cardiovascular Morbidity & Mortality: LIFE Study

Proportion of patients with first event(%) vs Serum uric acid (μM/L)

The estimated contribution of serum uric acid to losartan effect was 29% (p<0.004).
Serum Uric Acid Is Associated With New-Onset Diabetes in Hypertensive Patients With Left Ventricular Hypertrophy: The LIFE Study

Wiik BP et al, Am J Hypertens, 2010
Lifestyle modification & Insulin-sensitizing agents

Uric acid paradox
This concept is supported by the superior performance of antihypertensive therapy with thiazide diuretics in preventing heart failure.

ALLHAT Study, JAMA, 2002

Possible mechanism
- Different role between intracellular (pro-oxidant, NADPH oxidase) and extracellular UA (antioxidant)
UA, as an antioxidant

- UA can function as an antioxidant
  - by scavenging various reactive oxygen species, itself
  - by promoting SOD activity

- Systemic UA administration
  - Increase plasma antioxidant capacity at rest
  - Reduce exercise-associated oxidative stress
  - Improve endothelial dysfunction
Still Controversy…

Benefits of lowering UA is due to..

Reduction of UA per se!

vs.

XO inhibitors with related reduction of ROS
The bottom line is...

- *Increasing evidence indicates that UA may have a causal role in HTN*

- However, more studies are needed to dissect out the potential mechanisms

- Need more clinical trials to confirm a benefit of lowering UA on blood pressure
경청해 주셔서 감사합니다

論語(논어) 雍也篇(오야편)의 '어진 사람은 산을 좋아하고 지혜로운 사람은 물을 좋아한다.'는 知者樂水 仁者樂山(지자요 수 인자요산)의 줄임 말이다.