Uric acid and its Role in Hypertension and Renal Disease

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Disclaimer: Dr Johnson is an inventor on a patent with the University of Washington and Merck for allopurinol as a treatment of hypertension
Gout, a Partner in Cardiovascular Disease

- Hypertension 50-60%
- Obesity 60-80%
- Metabolic Syndrome 70-80%
- Chronic Kidney Disease 50-100%
- Cardiovascular Disease
Is Hyperuricemia an Independent Risk Factor?

**Independent**
- Atherogene
- CASTEL
- Chicago Heart Association Detection
- Framingham 1988
- Gothenburg
- Heart Institute of Spokane
- Hypertension Detection Followup Program
- Honolulu Heart
- MONICA
- NHANES I
- PIUMA
- Rotterdam
- SHEP
- Syst-China
- Worksite

**Not Independent**
- ARIC
- British Regional Heart Study
- Coronary Drug Project Report Group
- European Working Party
- Framingham 1999
- Iceland
- Social Institute of Finland
- Syst-Eur

**Meta-analyses for CHD Incidence**

Uric acid is independent risk factor RR 1.09 (CI 1.03-1.16) (26 studies, 402,997 subjects)  
*Arthritis Care Res* 2010; 62:170-180

Uric acid is independent risk factor  RR 1.13 (CI 1.07-1.30) (16 studies, 164,000 subjects) but was not significant in the 8 better performed studies (RR 1.02, CI 0.91-1.14)  
Uric Acid: A Product of Purine Metabolism

Purines

Xanthine

Xanthine oxidase

Uric Acid

Urate oxidase (Uricase)

Allantoin

Mutation

Man and Great and Lesser Apes

Other mammals
A Model of Mild Hyperuricemia

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

Uricase inhibitor
Oxonic acid (OA)

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

Hypertension 2001;38:1101-6
Chronic Hyperuricemia Increases Blood Pressure

- Low Salt Diet (LSD)*
- LSD/Oxonic Acid

*S LSD = 0.125% NaCl, ** p<0.05

Hypertension 2001;38:1101-6
Allopurinol Prevents BP Increase in Hyperuricemic Rats

Hypertension 2001;38:1101-6
Hyperuricemia Increases Renin Expression

Mazzali et al. Hypertension 38:1101-1106, 2001
Uric acid Lowers Endothelial NO Levels

Nakagawa et al, Am J Physiol 2006; 290:F625-631
Acute Cellular Effects of Uric acid

Oxidants

Uric Acid

Control

Inflammation (MCP-1)

Angiotensin II

Hypertension 2003; 41: 1287-93
Kidney Int 2005; 267: 1739-42
Am J Physiol 2002; 282: F991-7
J Hypertens 2010; 28: 1234-42
Hyperuricemia Induces Preglomerular Vascular Disease

Mazzali et al, AJP Renal Physiol 282:F991, 2002
“[My view] is that the [renal] arterial and arterial sclerosis are primary, but of unknown origin, and that … the vascular disease… produces disturbances of intrarenal hemodynamics ….that determines hypertension”

Goldblatt H. Physiol Reviews 27:120-165, 1947
Hypothesis

Could salt-sensitivity be the consequence of acquired renal injury?

NEJM 346:913, 2002

Mechanisms of Disease

SUBTLE ACQUIRED RENAL INJURY AS A MECHANISM OF SALT-SENSITIVE HYPERTENSION

RICHARD J. JOHNSON, M.D., JAIME HERRERA-ACOSTA, M.D., GEORGE F. SCHREINER, M.D., PH.D., AND BERNARDO RODRÍGUEZ-ITURBE, M.D.

IN 1856 Ludwig Traube proposed a role of the kidney in the pathogenesis of hypertension on the basis that hypertension and vascular disease were often associated with chronic Bright’s disease.
Models of Salt-Sensitive Hypertension

**Sympathetic Nervous System Overactivity**
- Model: phenylephrine infusion

**Increased Renin-Angiotensin**
- Model: Ang II infusion
  - Page Kidney

**Endothelial Dysfunction**
- Model: L-NAME

**Toxins**
- (Pb, CSA)
  - Model: CSA
  - Pb hypertension

**Aging**
- Model: Aging Rat

**Genetic**
- Model: SHR, Dahl S

**Metabolic (low K)**
- Model: hypokalemia

**Systemic hypoxia**
- Model: hypobaric hypoxia

**Microvascular Disease**

**Interstitial Inflammation**

**Sodium sensitive Hypertension**

**Low Nephron Number**
- Model: Maternal malnutrition
Does the Arteriolopathy Occur Independently of Blood Pressure?

Systolic Blood Pressure

OA2%

HCTZ

Arteriolar thickness (µm)

control OA OA-HCTZ OA-AP

Human Vascular Smooth Muscle Cells Express the Urate Transporter, URAT-1

Urate Uptake in VSMC

Uric acid Stimulates Human VSMC but inhibits Endothelial Cell Proliferation

Hyperuricemia Induces Salt-sensitivity

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

Biopsy:
arteriolopathy

Hypertension 40:355, 2002

Hypertension 40:355, 2002

Systolic BP (mmHg)

0 100 110 120 130 140 150 160

Time (weeks)

0 3 4 6 7 8 9 10

Oxonic acid stopped
LS +2% OA
LS
LS
LS

Biopsy:
arteriolopathy
HS

* # #

HS

LS
Hyperuricemia Induces Salt-sensitivity

- Uric acid dependent
- Salt resistant
- Renin and NO dependent
- No renal structural changes

- Uric acid independent
- Salt sensitive
- Volume dependent
- Kidney: arteriolosclerosis and inflammation

Hypertension 40:355, 2002
Is there Clinical Evidence for a Role of Uric acid in Hypertension?
## Serum Uric Acid Predicts Hypertension

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Israeli Heart Study (Khan, 1972)</td>
<td>10,000 males</td>
<td>2-fold risk at 5 YRS</td>
</tr>
<tr>
<td>Kaiser Permanente (Selby, 1990)</td>
<td>2,062 subjects</td>
<td>2-fold risk at 6 YRS</td>
</tr>
<tr>
<td>Univ of Utah (Hunt, 1991)</td>
<td>1482 adults</td>
<td>2-fold risk at 7 YRS</td>
</tr>
<tr>
<td>Olivetti Heart Study (Jossa, 1994)</td>
<td>619 males</td>
<td>2-fold risk at 12 YRS</td>
</tr>
<tr>
<td>CARDIA study (Dyer, 1999)</td>
<td>5115 adults</td>
<td>2-fold risk at 10 YRS</td>
</tr>
<tr>
<td>Osaka Health Survey (Taniguchi, 2001)</td>
<td>6,356 males</td>
<td>2-fold risk at 10 YRS</td>
</tr>
<tr>
<td>Hawaii-Los Angeles-Hiroshima Study (Imazu, 2001)</td>
<td>140 males</td>
<td>3.5-fold risk at 15 YR</td>
</tr>
<tr>
<td>Osaka Factory Study (Masuo, 2003)</td>
<td>433 males</td>
<td>1.0 mg/dl UA predicts ↑27 mm Hg at 5 YR</td>
</tr>
<tr>
<td>Osaka Health Survey (Nakanishi, 2003)</td>
<td>2310 males</td>
<td>1.6-fold risk at 6 YRS</td>
</tr>
<tr>
<td>Okinawa (Nagahama, 2004)</td>
<td>4489 adults</td>
<td>1.7-fold risk at 13 YRS</td>
</tr>
<tr>
<td>Bogalusa Heart (Alper, 2005)</td>
<td>679 children</td>
<td>Increased risk at 11 YRS</td>
</tr>
<tr>
<td>Framingham (Sündstrom , 2005)</td>
<td>3329 adults</td>
<td>1.6-fold at 4 YRS</td>
</tr>
<tr>
<td>Normative Aging Study (Perlstein, 2006)</td>
<td>2062 males</td>
<td>1.5-fold at 21 YRS</td>
</tr>
<tr>
<td>MRFIT (Krishnan, 2007)</td>
<td>3073 men</td>
<td>1.8-fold at 6 YRS</td>
</tr>
<tr>
<td>ARIC (Mellen, 2006)</td>
<td>9,104 adults</td>
<td>1.5-fold at 9 YRS</td>
</tr>
<tr>
<td>Nurse Health Study (Forman, 2009)</td>
<td>1500 women</td>
<td>1.89 fold at 5 years</td>
</tr>
<tr>
<td>Health Professional Followup (Forman, 2007)</td>
<td>750 men</td>
<td>1.08-fold at 8 YRS* (Not significant)</td>
</tr>
</tbody>
</table>
Serum Uric Acid in Adolescents with Hypertension

Feig and Johnson, Hypertension 42:247-252, 2003
Relationship Between SBP and Serum Uric Acid in Adolescents

Systolic BP (mm Hg)

Uric Acid (mg/dl)

R = 0.80

Feig D and R Johnson
Hypertension 2003; 42:247-252
Effect of allopurinol vs placebo in newly diagnosed hypertension in adolescents

- Randomized double-blinded placebo controlled cross-over design
- 30 Children 11-17yr old, new diagnosis essential hypertension
- Uric acid >6mg/dl
- Pharmacologically naive
- Allopurinol 200mg bid vs. placebo
- Four week medication phases with 2 week washout between arms

Feig et al, JAMA 2008; 300:924-32
Effect of allopurinol vs placebo in newly diagnosed hypertension in adolescents

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>$15.1 \pm 2.1$ yrs</td>
</tr>
<tr>
<td>% Male</td>
<td>60%</td>
</tr>
<tr>
<td>Weight</td>
<td>$97 \pm 23$ kg</td>
</tr>
<tr>
<td>BMI</td>
<td>$33 \pm 6.5$ kg/m²</td>
</tr>
<tr>
<td>Race</td>
<td>White 46%, Hispanic 23%, African American 31%</td>
</tr>
<tr>
<td>Uric Acid</td>
<td>$6.9 \pm 1.2$ mg/dL</td>
</tr>
</tbody>
</table>

Feig et al, JAMA 2008 Aug 27;300(8):924-32
Lowering Uric Acid Reduces SBP in Adolescents with Hypertension

In Subjects whose Uric acid was reduced to < 5 mg/dl, 86% (19/22) became normotensive versus 3% (1/30) controls
Could Uric acid have a role in the Epidemic of Hypertension?
Hypertension is Increasing

The Gout Epidemic

Mean uric acid (mg/dl)

- 1920: 3.5
- 1950: 5
- 1960: 5.5
- 1970: 6
- 1980: 6.5
# Patterns of Food Intake in the USA

<table>
<thead>
<tr>
<th></th>
<th>1980</th>
<th>1990</th>
<th>2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>RED MEAT (lbs)</td>
<td>126</td>
<td>112</td>
<td>114</td>
</tr>
<tr>
<td>MILK (gallons)</td>
<td>27.6</td>
<td>25.7</td>
<td>22.5</td>
</tr>
<tr>
<td>SWEETENERS (lbs)</td>
<td>123</td>
<td>132</td>
<td>149</td>
</tr>
<tr>
<td>Sugar</td>
<td>84</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>High Fructose corn syrup</td>
<td>19</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td><strong>Fructose (total)</strong></td>
<td><strong>52</strong></td>
<td><strong>57</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

*US Census Bureau, Statistical Abstract of the US, 2003, no 214*
Sugar and Fructose

• **Sugar (sucrose)** consists of a disaccharide of glucose and fructose

• **High fructose corn syrup (HFCS)** is a mix of 55% fructose and 45% glucose

• Fructose and to a lesser extent, sucrose, are also present in honey and fruit (especially fruit juices and dried fruits)
Fructose Metabolism

Fructose is produced from honey, fruits, high fructose corn syrup, and sucrose. Fructose is transported by Glut 5 transporter and undergoes fructokinase reaction to form fructose-1-phosphate. ATP depletion occurs during this process. Fructose-1-phosphate can be converted to glucose, glycogen, triglycerides, uric acid, xanthine, and xanthine oxidase.
Fructose Acutely Increases Serum Uric Acid

Fructose (1 g/kg body wt) increases serum uric acid within 30 minutes

Lancet 1970; 2:1310-1311
Soft Drink Consumption is Increasing

Nielsen and Popkin

Third National Health and Nutrition Exam Survey
Choi et al Arth Rheum 2008; 59:109-16
Could Sugar be a True Risk Factor for Hypertension?
Fructose Induced Hypertension is Improved with Xanthine oxidase inhibitor (Febuxostat)

High Fructose Intake from Added Sugars is associated with Increased Risk of Elevated BP

Risk for elevated BP in those with high (>74 g/d) vs low fructose (<74 g/d) intake in NHANES III

Jalal et al, J Am Soc Nephrol 2010; July issue
**Fructose Raises Blood Pressure in Humans**

*Males, 24 years old, given 60 g fructose or glucose*

Fructose-induced Ambulatory BP Rise is blocked by Allopurinol

74 men randomized to fructose (200g/d) or fructose plus allopurinol for two weeks

Perez-Pozo et al Int J Obesity 2010; 34: 454-61
What is the Role of Uric acid in Renal Disease?
Hyperuricemia Causes Glomerular Hypertension in Rats

Hyperuricemia Causes Glomerular Hypertrophy

Nakagawa et al, Am J Neph 2003; 23:2-7
Hyperuricemia Causes Glomerulosclerosis

Nakagawa et al, Am J Neph 2003; 23:2-7
Role of Uric acid in Renal Progression

Groups:

- Sham
- Remnant Kidney (RK)
- RK + Hyperuricemia (RK-OA) (induced by the uricase inhibitor, oxonic acid)
- RK –OA and Allopurinol (RK-OA-AP)

Role of Uric acid in Renal Progression

Kang et al, JASN 2002; 13:2888-97
Hyperuricemia Induces Vascular Disease in Rats with Kidney Disease

Fructose Induced Renal Microvascular Disease and Glomerular Hypertension

Fructose-induced Hyperuricemia causes Systemic and Glomerular Hypertension

Fructose Accelerates Renal Disease in the Remnant Kidney

![Control Diet](image1.png) ![Glucose Diet](image2.png) ![Fructose Diet](image3.png)

<table>
<thead>
<tr>
<th>Diet</th>
<th>Proteinuria, mg/dl</th>
<th>C_{Creatinine}, ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>33±5.7</td>
<td>1.23±0.04</td>
</tr>
<tr>
<td>Glucose</td>
<td>35±7.5</td>
<td>1.16±0.08</td>
</tr>
<tr>
<td>Fructose</td>
<td>73±15.4*</td>
<td>0.96±0.08*</td>
</tr>
</tbody>
</table>

Fructose Induces Inflammation in the Proximal Tubule

Cirillo et al, JASN 2007
Fructose causes Tubular injury in the Rat

University of Colorado Investigators

Miguel Lanaspa Taka Nakagawa
Gabriela Garcia Takuji Ishimoto Diana Jalal Tomoki Kosugi Miguel Lanasp ga
Taka Nakayama Chris Rivard Carlos Roncal Gaby Sanchez-Lozada Michiko Shimada Katsuyuki Tanabe