On the Origin of Obesity, Diabetes and Chronic Kidney Disease

Richard J Johnson MD
University of Colorado

The Research Discoveries of Dr Johnson’s Group has Led to Commercial Interest:

• Patents and patent applications
• Consultations: Danone
• Grants: Amway, Danone, NIH, and the State of Colorado
• Board Membership: Amway
• Lay Books: The Sugar Fix (Rodale), The Fat Switch (Mercola.com)
The Thrifty Gene Hypothesis, Revisited

This lecture is dedicated to James V Neel and William Oliver

The Anthropologist
James Neel Collecting blood from a Yanomamo Indian
Could a Survival Gene associated with Prehistoric Famine be the Cause of Diabetes Today?

Diabetes Mellitus: A “Thrifty” Genotype Rendered Detrimental by “Progress”?

JAMES V. NEEL
Department of Human Genetics,
University of Michigan Medical School,
Ann Arbor, Mich.

One in Six U.S. Youths are Obese
Obesity: An Ever Expanding Problem

Obesity defined as BMI >30


Florida

- 1995 14.3 % were obese
- 2012 26.6% are obese
- 2030 Projections 58.6% will be obese
The Precursor to Diabetes: Metabolic Syndrome

- Truncal obesity
- Impaired fasting glucose (insulin resistance)
- Elevated triglycerides
- Low HDL cholesterol
- Elevated blood pressure

- Other (Fatty Liver, elevated uric acid, microalbuminuria, elevated CRP, endothelial dysfunction, oxidative stress)
Sugar Intake Correlates with Obesity

Sugar intake per year:
- 1700: 4 lbs
- 1800: 18 lbs
- 1900: 90 lbs
- 2000: 155 lbs

Sugar Consumption Kilograms/Individual

Year

Sugar intake

Obesity rate

HFCS introduced

Sugar and Fructose

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

• **High fructose corn syrup (HFCS):** 55% fructose and 45% glucose as monosaccharides

• **Fructose** is also present in honey and fruit (especially fruit juices and dried fruits)
Role of Fructose in Obesity

Ishimoto T et al  PNAS 2012
Fructose Induces Metabolic Syndrome in Rats

Nakagawa et al, Am J Physiol 2006; 290:F625-631
Fructose and Metabolic Syndrome

**Brain**
- Activates taste centers
- Addicting behaviors (dopaminergic and opioid receptors)
- Leptin resistance
- Neurostimulant

**Liver**
- Fatty liver
- Elevated triglycerides
- ATP depletion
- Inflammation
- Uric acid generation

**Vasculature**
- Inflammation
- Endothelial dysfunction

**Kidney**
- Renal vasoconstriction
- Glomerular hypertension
- Renal injury
- Renal inflammation

**Adipocyte**
- Oxidative stress
- Inflammation
- Reduced adiponectin

**Metabolic Syndrome**
- Insulin resistance
- Elevated blood pressure
- Abdominal obesity
- Dyslipidemia
- Fatty Liver
- Inflammation
- Oxidative stress
- Endothelial dysfunction
- Hyperuricemia

**Type II Diabetes**

*Johnson et al, End Rev 2009;30:96-116*
Effect of Fructose (200 g/d) for 2 weeks on Metabolic syndrome in Men: Menorca Study

<table>
<thead>
<tr>
<th>Metabolic Syndrome (NCEP-ATPIII)(%)</th>
<th>Baseline 19%</th>
<th>Change 44%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>136 ± 15</td>
<td>55±20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>46.5 ± 1.5</td>
<td>-2.5 ± 0.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin resistance (HOMA)</td>
<td>1.7 ± 0.2</td>
<td>0.57 ± 0.16</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.3 ± 2.3</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>29.0 ± 0.6</td>
<td>0.2 ± 0.1</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>24 hr Systolic BP (mm Hg)</td>
<td>126±2</td>
<td>7 ± 2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 hr Diastolic BP (mm Hg)</td>
<td>75 ± 2</td>
<td>5 ± 3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.2 ± 0.2</td>
<td>1.1 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Perez-Pozo et al Int J Obes 2010
Fatty Liver Can be Induced by Sucrose Even with Caloric Restriction

Oil Red O Stain for Fat

Sprague Dawley rats fed sucrose or starch diet for 4 months at 90% of normal intake

Roncal-Jimenez C et al  Metabolism 2011
Fructose Metabolism

Fructose Has a Unique Nucleotide Degradation Pathway
Fructokinase Knockout Mice are Protected from Metabolic Syndrome

Ishimoto T et al  PNAS 2012; 109: 4320-4325
Fructose Metabolism

- Two isoforms: A and C

- Honey, Fruits
- High Fructose Corn Syrup
- Sucrose

- Fructose
  - Glut 5 Transporter
  - Fructokinase
  - ATP depletion

- Fructose-1-phosphate
  - Glucose
  - Glycogen
  - Triglycerides

- Uric acid

- ATP
- ADP

- AMP
- IMP
- Xanthine
- Xanthine oxidase
Fructokinase Isoforms

Fructokinase A and fructose
Fructokinase C and fructose

Ishimoto T et al  PNAS 2012; 109: 4320-4325
Fructokinase-A Knockout Develops Worse Metabolic Syndrome

Ishimoto T et al  PNAS 2012; 109: 4320-4325
Blocking AMPD2 Prevents Fructose-Induced Fat Accumulation

Triglycerides

Human HepG2 cells silenced for AMPD are protected from fructose (5 mM) induced Triglyceride Accumulation, 72 h

Lanaspa et al. PLOS One 2012
A Molecular Switch for Obesity

Lanaspa et al, PLOS One 2012
Fructose Metabolism

- Honey, Fruits
- High Fructose Corn Syrup
- Sucrose

Fructose

Glut 5 Transporter

Fructose

Fructokinase

ATP depletion

Fructose-1-phosphate

Gluco 5 Transporter

Fructose

ATP

ADP

AMP

AMP Deaminase

IMP

Xanthine

Xanthine oxidase

Uric acid

Glucose

Glycogen

Triglycerides
Uric acid Causes Mitochondrial Oxidative Stress in Cultured Hepatocytes

Lanaspa MA and Sanchez-Lozada, J Biol Chem in press
Uric acid Increases Fat in Hepatocytes

Mitochondria

- Inhibit Aconitase in Kreb Cycle
- Citrate Enters Cytoplasm
- Inhibit ECOH in β-fatty acid cycle
- Increased Fat Synthesis
- Block Fat Oxidation

Lanaspa MA et al, J Biol Chem 2012
Uric acid Stimulates Lipid Accumulation in HepG2 Cells

Lanaspa MA, Sanchez Lozada LG, and Kang DH, J Biol Chem in press
Lowering Uric acid Prevents Fatty Liver from Fructose

\[ N = \text{Control Diet}; \ F = \text{Fructose 20\% in water}; \ AP = \text{allopurinol (lower uric acid)} \]
Fructose Acutely Increases Serum Uric Acid

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

Lancet 1970; 2:1310-1311
Gout, the Disease of Kings and King of Diseases
Gout, a Partner in Cardiovascular Disease

- Hypertension 50-60%
- Obesity 60-80%
- Metabolic Syndrome 70-80%
- Chronic Kidney Disease 50-100%
- Cardiovascular Disease
Role of Fructose and Uric acid

• Hypertension
• Metabolic Syndrome and Diabetes
**Fructose Raises Blood Pressure in Humans**

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

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*Am J Physiol Regul Integr Comp Physiol 294: R730-R737 2008;*
Fructose Induced Hypertension is Improved by Lowering Uric acid

Uric acid induces Oxidative Stress in Human Endothelial Cells

Yu M, Kang DH and others
J Hypertens 2010 Jun;28(6):1234
## 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>MRFTT (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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>$15.1 \pm 2.1 \text{ yrs}$</td>
</tr>
<tr>
<td><strong>% Male</strong></td>
<td>60%</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>$97 \pm 23 \text{ kg}$</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>$33 \pm 6.5 \text{ kg/m}^2$</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td>White 46%</td>
</tr>
<tr>
<td></td>
<td>Hispanic 23%</td>
</tr>
<tr>
<td></td>
<td>African American 31%</td>
</tr>
<tr>
<td><strong>Uric Acid</strong></td>
<td>$6.9 \pm 1.2\text{mg/dL}$</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

Feig et al, JAMA 2008 Aug 27;300(8):924-32
Role of Fructose and Uric acid

- Hypertension
- Metabolic Syndrome and Diabetes
Allopurinol Improves Insulin Resistance and Dyslipidemia in Fructose-fed Rats

Triglyceride

Fasting insulin

Nakagawa et al, Am J Physiol 2006; 290:F625-631
## Uric Acid Predicts Development of Hyperinsulinemia or Diabetes

**Johnson et al, Endocrinol Rev 2009**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>F/U</th>
<th>Independent</th>
<th>RR (C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARIC</td>
<td>9,020 adults</td>
<td>11 YRS</td>
<td>Yes</td>
<td>1.3 (1.2-1.4)</td>
</tr>
<tr>
<td>Spokane</td>
<td>60 adults with MI</td>
<td>6 MOS</td>
<td>Yes</td>
<td>5.47 (1.6-17.7)</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>4,536 adults</td>
<td>10 YRS</td>
<td>Yes</td>
<td>1.68 (1.22-1.30)</td>
</tr>
<tr>
<td>Framingham</td>
<td>5,209 adults</td>
<td>26 YRS</td>
<td>Men</td>
<td>2.3 (men) and 2.1 (women)</td>
</tr>
<tr>
<td>Osaka</td>
<td>2,310 adult men</td>
<td>6 YRS</td>
<td>Yes</td>
<td>1.78 (1.11-2.85)</td>
</tr>
<tr>
<td>Osaka</td>
<td>6,356 men</td>
<td>9 YRS</td>
<td>No</td>
<td>1.24 (0.9-1.7)</td>
</tr>
<tr>
<td>Mauritius</td>
<td>2,605 adults</td>
<td>5 YRS</td>
<td>Yes</td>
<td>1.37 (1.20-1.57)</td>
</tr>
<tr>
<td>Britain</td>
<td>7,735 men</td>
<td>12.8 YRS</td>
<td>Yes</td>
<td>1.5 (0.9-2.5)</td>
</tr>
<tr>
<td>Sweden</td>
<td>766 men</td>
<td>13.5 YRS</td>
<td>Yes</td>
<td>5.8 (2.2 - 16.0)</td>
</tr>
<tr>
<td>Kinmen</td>
<td>641 adults</td>
<td>7 YRS</td>
<td>Women</td>
<td>1.44 (1.13-2.25)</td>
</tr>
<tr>
<td>Finland</td>
<td>522 adults</td>
<td>4.1 YRS</td>
<td>Yes</td>
<td>1.87 (1.07-3.26)</td>
</tr>
<tr>
<td>Mauritius</td>
<td>4259 adults</td>
<td>5 YRS</td>
<td>Men</td>
<td>1.37 (1.11-1.68)</td>
</tr>
<tr>
<td>Nauru</td>
<td>266 adults</td>
<td>6 YRS</td>
<td>Women</td>
<td>Not given</td>
</tr>
<tr>
<td>Israel</td>
<td>10,000 men</td>
<td>5 YRS</td>
<td>Yes</td>
<td>1.35</td>
</tr>
<tr>
<td>China</td>
<td>2609 adults</td>
<td>9 YRS</td>
<td>Yes</td>
<td>1.4 (1.02-1.92)</td>
</tr>
</tbody>
</table>
Uric acid Induces a Diabetic Phenotype in Adipocytes

Allopurinol Reduces Fat Inflammation in Pound Mice with Metabolic Syndrome

*Lean Mouse*  
*Obese Mouse*  
*Obese Mouse + Allopurinol*

Sautin et al,  
Diabetes 2011
Sucrose Induces Pancreatic Islet Injury

Islet (PAS)  Macrophage  Insulin Stain

STARCH

SUGAR

Roncal-Jimenez et al. Metabolism 2011
Could Uric acid be Responsible for Islet Injury?

Expression of Urate Transporter in Islets (URAT)  Oxidative Stress (DCF)

**STARCH**

**SUGAR**

*Roncal, Lanaspa, Metabolism 2011*
Uricase Mutation in Mammals

1. Purines
2. Xanthine
3. Uric Acid
4. Xanthine oxidase
5. Urate oxidase (Uricase)
6. Allantoin
7. Other mammals
8. Man and Great and Lesser Apes

Mutation
The Miocene and the First Apes

Proconsul, 22 MYA
Early Miocene Apes were Fruit Eating and Lived in Lush Tropical Rain Forests in Africa (20-15 MYA)
An “Excursion” to Europe 17 Million Years Ago

Crossing the landbridge into Eurasia across the Tethys Sea

16.5 MYA

Begun DR Science 2000; 287; 2375a
Apes Retreat to Isolated Sites with Global Cooling

Andrews and Kelly  Folia Primatol 2007: 78:328-343
Evidence for Recurrent Periods of Starvation in *Dryopithecus* in Spain

*Repetitive linear enamel hypoplasia*

*Repetitive Linear Enamel Hypoplasia shows recurrent periods of Food Shortage (stress) During Primate Growth*

*Canines from Orangutan*

Migration of European Apes “Back to Africa”

European Great Apes

Asian Great Apes

African Apes and Humans

8 to 13 MYA

Andrew and Kelly  Folia Primatol 2007: 78:328-343
Dual Mutations in Uricase in the Miocene
Fructose and Survival

↑Fat stores (fatty liver, triglycerides)
↑Insulin resistance (↑glucose for the brain)
Leptin resistance (neural effects)
↑BP and ↑Salt sensitivity (Renal effects)

Fruit (fructose)

Autumn

Winter

Summer

Spring

Starvation
Fructose: A Survival Factor

- Less fruit available
- Uricase mutation
- Longer period of starvation
- Autumn
- Winter
- Spring
- Summer

- ↑↑BP and ↑Salt sensitivity (Renal effects)
- ↑↑Fat stores (fatty liver, triglycerides)
- ↑↑Insulin resistance (↑glucose for the brain)
- ↑↑Leptin resistance (neural effects)

Johnson and Andrews Evol Anthropol 2010
Uricase Inhibition Amplifies the Ability of Fructose to Increase Uric acid Levels

A Rat given fructose shows a much higher rise in serum uric acid when uricase is inhibited

Stavric et al Experientia 1976; 32:373
Uricase Inhibition Increases Fructose Effects

Rats were given soft drinks consisting of 7% Fructose and 3% glucose

Sanchez-Lozada LG, Am J Physiol 2013
Uric acid is higher in Western Culture

Yanomamo Indian

The Fat Switch, 2012, Mercola.com
Venus Figurines, Fertility and Beauty

The Venus of Gagarino
Ukraine, 22,000 B.C.
Venus Figurines: Obesity Related to Honey?
New Guinea, 8000 Years Ago

Saccharum officinarum: The Noble Cane
The Spread of Sugar Cane
Obesity = Medoroga
Diabetes = Madhumeha
Angina = Hritshoola

Diabetes develops in the individual who follows “sedentary pursuits or is in the habit of taking sweet liquids”

Sushruta Samhita, 400 A.D.

The Fat Switch, 2012, Mercola.com
Sugar and Royalty: Adipose Rex

Emperor Vitellius of Rome  69 A.D.
King Charles the Fat, Holy Roman Emperor, 888 A.D.
Sancho the Fat, King of Léon (NW Spain and Portugal)  966 A.D.
Sactius the Fat, King of Spain  1000 A.D.
William the Conqueror (1066-1087 A.D.)
Louis VIth (Louis the Fat), King of France  1137 A.D.
King John of England (1199-1216 A.D.)
Saint Thomas Aquinas of Italy  1225-1274 A.D.
Pope “Fat” Leo Xth  1521 A.D.
King Henry VIIIth  1532 A.D.
Louis the XVIIIth of France (1755-1824)
King “Fat” Frederick I of Württemberg  1806 A.D.
Sugar Plantations in Hispaniola
Sugar Intake Rises in England

Sugar Imports/Exports in England (1660-1753)

Sugar Intake in England 1660-1753

Sidney Mintz  Sweetness and Power  1985
Sugar per capita intake rises in England

“For one fat person in France or Spain, there are a hundred in England”

William Wadd 1816
Emergence of Obesity

1660  Obesity  Tobias Venner

1670  Diabetes  First modern description of diabetes  Thomas Willis

1768  Coronary Artery Disease  William Heberden

1827  Chronic kidney Disease  Richard Bright

1874  Hypertension  Frederick Mahomed
The Evolution of Man

The Economist, December 2003