New Prevention Targets for Gout and Comorbidities: Epidemiologic Perspectives

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Disclosure

• None
Gout - “morbus dominorum et dominus morborum”

• “Disease of Kings and King of Diseases,”

• Known since antiquity – described by Hippocrates

• “the Patrician Malady”

• Originally a disease of the affluent; middle aged men of the wealthy upper class
# Prevalence of Gout in US and Canada

**US Data:** Based on NHANES III (1988-94)

<table>
<thead>
<tr>
<th>Age</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.2%</td>
<td>2%</td>
<td>2%</td>
<td>6%</td>
<td>9%</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Women</td>
<td>0.6%</td>
<td>0.1%</td>
<td>0.6%</td>
<td>2%</td>
<td>4%</td>
<td>5%</td>
<td>6%</td>
</tr>
</tbody>
</table>

(Total = 8.3 mil) in 2007-2008)  

**Canada Data (BC):** Based on physician codes, 2004

<table>
<thead>
<tr>
<th>Age</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>≥80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>0.4%</td>
<td>1%</td>
<td>3%</td>
<td>6%</td>
<td>9%</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Women</td>
<td>0.2%</td>
<td>0.6%</td>
<td>1%</td>
<td>2%</td>
<td>4%</td>
<td>5%</td>
<td>7%</td>
</tr>
</tbody>
</table>

(Total = 0.83 mil [men = 0.58 mil; women = 0.25 mil])
Relation between Serum Urate Levels and Incidence of Gout.

<table>
<thead>
<tr>
<th>NHANES 1999-2008</th>
<th>Mean Serum Urate Level, mg/dL (µm/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>All</td>
</tr>
<tr>
<td>20-29</td>
<td>5.26</td>
</tr>
<tr>
<td>30-39</td>
<td>5.24</td>
</tr>
<tr>
<td>40-49</td>
<td>5.33</td>
</tr>
<tr>
<td>50-59</td>
<td>5.48</td>
</tr>
<tr>
<td>60-69</td>
<td>5.63</td>
</tr>
<tr>
<td>70-79</td>
<td>5.70</td>
</tr>
<tr>
<td>80+</td>
<td>5.84</td>
</tr>
</tbody>
</table>
Figure 5

DE NOVO SYNTHESIS

Ribose-5-P + ATP

PRPP synthetase

PRPP

IMP

Inosine

Hypoxanthine

Xanthine

Urate

+ PRPP

+ PRPP

+ PRPP

5'-nucleotidase

5'-nucleotidase

5'-nucleotidase

PNP

PNP

PNP

adenosine deaminase

ADENOSINE

ADENOSINE

ADENOSINE

Adenosine

AMP

ATP

GTP

SALVAGE PATHWAYS

Ethanol

Fructose Intolerance or Infusion

Glycogen Storage Diseases

(Type I, III, V, and VIII)

Severe Tissue Hypoxia

feedback inhibition

Mutation

Man and Great Apes

Other mammals

Cladogram of hominoid evolution showing the proposed times of the various uricase mutations.

Uricase, Diet, and Gout

- Humans – **only** mammals that develop gout spontaneously (likely due to hyperuricemia)
- Diet of the great apes (SUA, 1.5–3mg/dl) - **vegetation and fruits, with only small amounts** of animal protein
  » Similar to people in some indigenous human hunting and gathering societies.
- Gout **was rare among Africans**, esp in rural areas with agricultural and diary based diets. ➔ **Now ↑** frequency, esp urban communities. (Similar among US blacks now as compared with 1940’s and before)

*Johnson & Rideout, NEJM (2004)*
Prevalence ↑ - Immigration Studies

• The immigration to Western countries — associated with ↑ in serum Uric Acid (UA) levels and risk of gout
  » E.g. immigration of the Filipino and Japanese to North America
Prevalence (1-y) ↑ – US NHIS (per 1,000)

% prevalence

- 1969: 4.8
- 1976: 7.8
- 1988: 8.5
- 1996: 9.4
What factors contribute to this increase?

• **Dietary and lifestyle trends**
  » Western Diet
  » Red Meat, Sugary Soda, Refined CHO

• **Hyperuricemic conditions**: Obesity, metabolic syndrome, HTN, End Stage Renal Diseases

• Increased use of **meds** that ↑ urate levels: diuretics, low-dose ASA, certain organ transplantation medications

*References*

Prospective Cohort Studies for Gout

- Health Professionals Follow-Up Study (HPFS): 51,529 male health professionals aged 40-75 from 50 states followed since 1986
- Nurses Health Study (NHS): 121,700 female registered nurses aged 30-55 from 11 states followed since 1976
- By validated questionnaires
- Follow-up rate is > 90%
Purine-Rich Food Group and Gout - HPFS

P for trend = 0.016

P for trend = 0.779

Choi et al. NEJM 2004
Dairy Intake and Gout - HPFS

Choi et al. NEJM 2004

Dairy Intake Quintiles (serving/d)

Low-Fat Dairy Intake

High-Fat Dairy Intake

Multivariate Relative Risk

P for trend < 0.001

P for trend = 0.648
Sweetened Soft Drinks $\rightarrow$ Gout

**P for trend = 0.002**

Cohort Relative Risk

Choi et al. JAMA (2010)
Free Fructose $\rightarrow$ Gout

P for trend $<$ 0.001

Free Fructose Intake Quintile (% of energy)

Sugary Soda $\rightarrow$ $\uparrow$sUA Levels

*Choi et al. A&R (2008)*
Fructose-Induced UA Production

Choi et al, JAMA (2010)
### Table 1. Lifestyle Risk Factors of Hyperuricemia and Gout

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Risk of Hyperuricemia</th>
<th>Risk of Gout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiposity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Waist-to-Hip Ratio</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Weight Loss</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Purine-rich Foods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meats</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Seafoods</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Purine-rich Vegetables/Nuts</td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Alcohol</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Fructose</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sugar-Sweetened Beverages</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Sweet Fruits/Fruit Juices</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Coffee/Decaffeinated Coffee</td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Dairy Products</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-fat Dairy Products</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>High-fat Dairy Products</td>
<td></td>
<td>↔</td>
</tr>
<tr>
<td>Vitamin C Supplements</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Gout Risk and a Healthy Eating Pyramid

Symbols for Gout Risk (& Hyperuricemia)

- Risk Increase
- Risk Decrease
- Risk Neutral

Use Sparingly

White rice, white bread, potatoes, pasta, & sweets

1 to 2 servings
( Low-fat dairy products
High-fat dairy products
)

Fish, poultry and eggs

0 to 2 servings

Nuts and legumes

1 to 3 servings

Vegetables

In abundance

Fruit (Cherries)

2 to 3 servings

Whole grain foods

At Most Meals

Plant oils (olive, canola, soy, sunflower, peanut, & other vegetable oils)

At Most Meals

Dairy or calcium supplement

1 to 2 servings

Red meat & butter

Risk Increase

Risk Decrease

Risk Neutral

Multiple Vitamins

For Most (vitamin C)

Coffee

Tea

Sweetened Soda

Alcohol in moderation

Unless Contraindicated (wine, beer, liquor)

Dairy or calcium supplement

1 to 2 servings

Low-fat dairy products

High-fat dairy products

Risk Increase

Risk Decrease

Risk Neutral

DAILY EXERCISE AND WEIGHT CONTROL

Choi et al. NEJM (2004)
Choi et al. JAMA (2010)
Zhang et al A&R (2012)
Co-Morbidities of Gout

- The Metabolic Syndrome: 63% (NHANES)
- HTN: 74% (NHANES)
- Obesity: 53% (NHANES)
- Type 2 Diabetes: 26% (NHANES)
- CAD: 25% (GPRD), 18% (HPFS)
- CKD (≥ stage 3): 20% (NHANES)
- Kidney Stone: 14% (NHANES); 15% (HPFS)


General Practice Research Database (GPRD)
Health Professionals Follow-up Study (HPFS)
The National Health and Nutrition Examination Survey (NHANES)
Anti-HTN Agents and Gout Risk

- **↑ Risk:**
  - Diuretics: (RR=2.36)
  - β-blockers: (RR=1.48)
  - ACE-inhibitors: (RR=1.24)
  - Non-losartan ARB: (RR=1.29)

- **↓ Risk:**
  - Losartan: (RR=0.81)
  - Calcium channel blockers: (RR=0.87)

Potential Novel Targets for Gout Prevention

- Dairy Products (Low-fat)
- Decaf. Coffee (or regular coffee)
- Vitamin C (>500mg/dL)
- Cherries
- Weight Loss
- Losartan and Calcium Channel Blockers – HTN patients
- (Avoiding hyperuricemic risk factors: Red meat and fructose-rich beverages)
Stages of Gout

Asymptomatic Hyperuricemia

Intercurrent Gout (Early)

Intercurrent Gout (Frequent)

Chronic Tophaceous Gout

After Successful ULT Discontinuation

Role of Lifestyle Modification

The option to ↓urate and CVD comorbidities

The option to ↓urate and CVD comorbidities

Adjunct to ULT to ↓urate and CVD comorbidities

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Acknowledgements

• Participating Health Professionals & Nurses
• NIAMS, CIHR
• Arthritis Society of Canada
• Takeda (TAP)
Thank You