Lecture: Rheumatology

-Hyperuricemia & Gout as an Independent Risk Factor of Atherogenesis

Mitchell D. Forman, D.O.
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Name of CME Activity: ACOFP 62nd Annual Convention and Scientific Seminar

Dates and Location of CME Activity: March 12-15, 2015, The Cosmopolitan Las Vegas, Nevada
Lecture: Rheumatology
- Hyperuricemia & Gout as an Independent Risk Factor of Atherogenesis (Fordman)
- Update on DMARDS in Common Rheumatologic Diseases for the Family Physician (Harris)

Thursday, March 12, 2015 8:00-10:00 am

Name of Faculty/Moderator: Mitchell Foreman, DO

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Signature: Mitchell Foreman, DO

Date: 1/4/15

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Deadline: Monday, January 12, 2015

SPEAKER CV AND INTRODUCTION
Hyperuricemia & Gout as an Independent Risk Factor for Atherogenesis
Objectives

• Discuss the myths & realities regarding gout
• Discuss the factors associated with hyperuricemia & gout
• Review compelling data re: hyperuricemia & its strong association with hypertension, MI, stroke & CKD
• Reinforce an awareness that patients presenting with gout should be evaluated for other risk factors associated with ASCVD

Uric Acid

The Good

Intelligence
Alzheimer’s
Parkinson’s Disease

The Bad

Tophi
Gout
Stone

The Ugly

CVA
MI
What’s irrefutable?

Epidemiology

- Gout – most common form of inflam. arthritis in men > 40 yoa
- Prevalence of gout 2007-08 of 3.9%
  - 8 million persons w Gout
  - 10 yr inc of 45%
  - > 80 yoa, inc 100%
  - Uric acid levels have inc signif over last 80 yrs
- Inc sua is the most highly correlated lab value with the metab. syndrome

Risk of Gout by SUA

Risk of gout for a SUA > 9.0 mg% ~ 20% within 5 yrs


How Do We Know Who is at Risk for Future Gout Attacks?

- Pts who have had freq attacks will continue to have freq attacks
- Gout flares tend to recur & there is a pattern of inc freq. of attacks
- 60% of pts have a 2\textsuperscript{nd} attack w/in 1 yr
- > 80% will have a 2\textsuperscript{nd} attack w/in 3 yrs

Gout Attacks Twice as Likely at Night

- 2.36 – fold greater risk for nocturnal attacks
- Undertreated – 45% on allopurinol & 25% on colchicine
- Independent of alcohol or purine intake
- ? Lower body temp @ night, dehyd, periarticular dehyd or dec bld cortisol
- ? OSA – hypoxia inc nucleotide turnover (20%)

Choi, HK. Boston Online Gout Study: Arth & Rheum, Dec. 11, 2014

“Perfect Storm”
more severe & complex cases due to a convergence of factors

- Prevalence of HBP
- Use of diuretics
- Use of ASA
- Obesity
- Inc consumption of
  - Beer
  - Fructose
  - Corn syrup

- Inc life expectancy
- Ability to keep pts alive with:
  - CAD
  - CHF
  - DM
  - CKD
- Lack of effective therapy

Epidemiology: Disease Burden

• Gout is expensive – cost & work days
  • Tx failure gout (> 6 attacks/yr) = > $25,000
  • Added costs
    • ER & clinic visits
    • Hospitalizations
    • Mngt of comorbidities

• Loss of productivity
  • 81 pt, < 65 yoa, 1 yr : 30 – 60 workdays lost
  • Lost days of social activities & self care


Hyperuricemia & Gout

• Pathogenesis of hyperuricemia
  • Overproduction (10%)
    • HGPRTase /PRPP synthetase (1%)
    • Increased purine intake
    • Alcohol
    • Myeloproliferative Disease
    • Psoriasis
  • Underexcretion (90%)
    • renal defect, dec. GFR, diuretics, tubular toxins (alcohol, low dose ASA, cyclosporine), hypothyroidism, lead
Clinical Course of Classical Gout

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<tr>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
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<tr>
<td>Asymptomatic Hyperuricemia</td>
<td>Acute Intermittent Arthritis</td>
<td>Chronic Arthritis with Acute Exacerbations</td>
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- **Stage I:**
  - Asymptomatic
  - No Arthritis
  - Atherogenesis

- **Stage II:**
  - Acute Attacks 1-2 Weeks
  - Intervals 2-10 Years
  - Joints 1-2

- **Stage III:**
  - Acute Attacks 1 Week – 2 Months
  - Intervals 2-3 Wks, 3-4 Mos.
  - Joints 4-5
  - Tophi – Bone & Cartilage
  - Continuous Arthritis
  - Acute Attacks Superimposed

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Acute Gouty Arthritis

- Abrupt onset of monoarthritis
- Episodic disease
- Sudden changes in uric acid levels are best predictor
- Classically 1st attack is “podagra”
- Attacks polyarticular with time
- Needle shaped negatively birefringent MSU crystals
- Tophi indicative of chronic urate overload
Oligoarthritis

MSU Crystals

Light Microscopy

Polarized Microscopy

Compensated Polarized Microscopy

PGY
Management of Crystal Disease

- Clinical presentation
- Arthrocentesis – dx & tx
- NSAIDs
- Colchicine
- Corticosteroids - p.o., i.v.
- Uric Acid Lowering Agents
  - not during acute attacks!
Indications for Urate Lowering

- Tophaceous disease with erosions
- Uric acid nephrolithiasis
- Recurrent attacks despite prophylaxis
- Prevent Acute cell lysis - e.g., chemo.
- Allopurinol or febuxostat contraindicated in acute gout but do not stop during an attack
- Not for mild or asymptomatic hyperuricemia?

Pegloticase

**Mech of Action:** recombinant porcine-like uricase able to metabolize uric acid to allantoin. In contrast to rasburicase, it is pegylated with increased elimination half-life. Given by slow infusion q 2-4 wks.

**Indications:** Chronic refractory gout, i.e., failure to normalize serum uric acid & continued signs & sx despite xanthine oxidase inhibitors @ max. med. approp dose or for whom these drugs are contraindicated.

**Dosage:** 8 mg as a slow infusion q 2-4 wks mixed in 0.9 or 0.45 saline over 2 hrs
Alcohol & Gout

- Assoc. betw. consumption & SUA (1)
  - Liquor – 0.29mg/dL for each add serving
  - Beer – 0.46 mg/dL
  - Wine – no independent association

- Health Professionals follow-up study (2)
  - Beer - risk of gout inc 50% for each 12 oz
  - Liquor - risk of gout 15%
  - Wine – mod levels did not inc risk


Myth: Gout is common among men but rare among women

Reality

- Increases substantially after menopause & rises with age
- In kidney, URAT1 responsible for reabsorption of uric acid from proximal tubule
- Estrogen has a direct effect on expression

Myth: The uric acid is normal, it can’t be gout

Reality

• 339 pts (2 studies) comparing tx with etoricoxib or indometh for acute gout
• 14% uric acid < 6.0 mg/dL at baseline
• 32% < 8.0 mg/dL during acute attack
• A change in uric acid is a better predictor of acute gout than hyperuricemia


Are Cherries Now Ripe for Use as a Complementary Therapeutic in Gout

• One serving of cherries = ½ cup (~ 10-12)
• Risk reduction > in those consuming 2 or 3 servings/d
• Cherry intake + allopurinol = 75% lower incid
• Evid for anti-inflam properties of cherry anthocyanins & mod uric acid lowering rel to XO inhibition & ascorbate uricosuric effect
• ACR 2012 Gout Dietary Guideline:
  • alcohol, organ meats, high fructose corn syrup beverages & encourage low –fat dairy & veg.

What’s more controversial?

Hyperuricemia as an Independent Risk Factor for Atherogenesis
Dr. Nathan Smith Davis – 1887 AMA Address

“High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increases the tonus of the renal arterioles”

How can I prove that Hyperuricemia is a risk factor for atherosclerosis?

• Uric Acid pathologically assoc with vascular damage & inflamm.
• Data that hyperuricemia is associated with CVD & premature death from MI & stroke
• Lowering uric acid levels associated with reduced risk
Pathophysiology of Vascular Damage Due to Hyperuricemia
The Two Faces of Uric Acid

- Uric acid highest [ ] anti-oxidant in blood
- Provide > 50% of total anti-oxidant
- Anti-oxidant effect complex
  - Doesn’t react with some oxidants, e.g SO
- Effects in AS, CVA & MI?
  - Protective (compens) rxn vs primary cause
  - Activated by oxidative stress
  - Metab derangements - Cu++ & Fe++
Uric Acid: A new look at an old risk marker for CVD, metabolic syndrome & type 2 DM: The urate redox shuttle

• Role of UA, oxidative – redox stress, reactive O$_2$ species, dec endothelial nitric oxide & endothelial dysfunction cannot be over emphasized
• In the pro – oxidative environment, the antioxidant properties of UA paradoxically become pro – oxidant
• This contributes to the oxidation of lipoproteins within atherosclerotic plaques
• Elev of uric acid > 4 mg/ml should be a “red flag” to the inc risk of CVD & espec in those at risk for CVD

Hayden, MR & Tyagi SC. Nutrition & Metab. 2004; 1:10, 1 - 15

Uncontrolled hyperuricemia results in afferent arteriole with thick wall & small lumen (B). When urate normalized, arteriole thinner & the lumen larger (C).

Uric Acid, Vascular Smooth Muscle Cell Proliferation & Inflammation

• Uric acid induces COX-2, TXA2 & PDGF A, which induces vasc. smooth muscle cell proliferation

• Soluble u.a. is pro – inflammatory
  • Induces Mono. Chemoattract. Protein-1
  • MCP-1 is a chemokine important in vasc dx & atherosclerosis

• Soluble u.a. induces IL-1B, IL-6 & TNF-a


Is There a Pathogenetic Role for Uric Acid in Hypertension, Cardiovascular & Renal Disease?

• U.A. stimulates vascular smooth muscle cell proliferation & induces endothelial dysfunction

• U.A. stimulates the production of cytokines from leukocytes & chemokines from vascular smooth muscle cells (TNF, IL-1, IL -6)

• Hyperuricemia activates circulating platelets

• Mild hyperuricemia inhibits the nitric oxide system in the kidney → vasoconstriction

http://hyper.ahajournals. Org/cgi/content/full/41/6/1183
Clinical Data Supporting Hyperuricemia as a Risk Factor for Cardiovascular Disease

Comorbidities Associated with Hyperuricemia

- Renal manifestations\(^1\)
- Obesity\(^2\)
- Metabolic syndrome\(^3\)
- Diabetes mellitus\(^4\)
- Heart failure\(^5\)
- Hyperlipidemia\(^2\)
- Hypertension\(^6\)
- Cardiovascular disease\(^7\)

Studies demonstrating some associations with hyperuricemia and cardiovascular outcomes

<table>
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<tr>
<th>Finding</th>
<th>Supportive Study</th>
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| Hyperuricemia ↑ development of CV, IHD, and/or CHD | ✓ Breckenridge et al. (Lancet, 1996)  
✓ Framingham Heart Study (Am Intern Med, 1999) |
| Hyperuricemia ↑ risk of CV events | ✓ SHEP (J Hypertens, 2000)  
✓ Worksite Treatment Program (J Hypertens, 1996)  
✓ MUIMA (Hypertension, 2000)  
✓ LIFE 2003 (Kidney Int, 2000)  
✓ Darmawan et al (J Rheumatol, 2003)  
✓ Lehto et al (Stroke, 1998) |
| Hyperuricemia ↑ mortality from CHD, IHD, and overall mortality | ✓ NHANES (JAMA, 2000)  
✓ Framingham Heart Study (Ann Intern Med, 1999)  
✓ Bickel et al (Am J Cardiol, 2002)  
✓ Darmawan et al (J Rheumatol, 2003)  


Comorbidities of Gout & Hyperuricemia

VA population

- median # comorbidities in pts w gout: 3 – 4
- HBP > 90%
- Inc Lipids > 60%
- DM & CKD > 50%
- CAD > 45%

Comorbidities of Gout & Hyperuricemia

• Gout pts 80% inc risk of CHF
• Inc over time
• CHF pts with gout have inc mortality even when adjust for other risk factors


Comorbidities of Gout & Hyperuricemia

• NHANES study 2007 – 08: 5,707 pts
• 74% HBP
• 71% CKD stage 2 or >
• 53% obese
• 26% DM
• 14% MI
• 11% CHF
• 10% CVA
• Prev of comorb inc w degree of hyperuricemia

Uric Acid Level as a Risk Factor for CV & All – Cause Mortality in Middle – aged Men

- Pop. based prospective cohort study of 1,423 Finnish men w/o CVD, DM or CA
- Main outcome measure - death from CVD & any cause
- Mean f/u was 11.9 yrs; 157 deaths; 55 CV
- In age – adj analysis, sua in the upper 1/3 were assoc with a 2.5 – fold > risk of death from CVD than in the lower 1/3
- Men with sua levels in the upper 1/3 were 1.7 – fold more likely to die from any cause
- SUA is a strong predictor of CVD mortality in middle – aged men, independent of variables commonly assoc w gout or the metabolic syndrome.

Kaplan – Meier hazard curve for cardiovascular death in serum uric acid categories

Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study

- Compared losartan to atenolol for reduction in CV morbidity & mortality
- Losartan interferes with urate reabsorption
- > 9,000 pts w HBP & LVH followed for ~ 4.8 yrs
- Pts. generally not hyperuricemic on entry
- Baseline SUA found to be signif assoc with inc CV events
- Inc. SUA in atenolol gp signif > losartan gp (P < .0001)
- Estimated contribution of SUA to CV death, non-fatal & fatal MI, & fatal & non-fatal stroke was 29%
- Attenuating SUA reduces CV events in high risk gps

**Uric Acid is a Risk Factor for Myocardial Infarction & Stroke**

- 4,385 participants in Rotterdam, 1990-1993 were > 55 yoa, free from CVA & CHD
- Average f/u was 8.4 yrs
- Relationship betw SUA & risk of CVD is linear
- High SUA levels assoc with risk of MI & CVA
- Age & sex adjusted hazard ratios for highest vs lowest quintile of UA were
  - 1.68 CVD
  - 1.87 MI
  - 1.57 CVA
- **SUA is a strong risk factor for MI & stroke**


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**Independent Impact of Gout on Mortality and Risk for Coronary Heart Disease**

- Prospectively examined 51,297 males in the HPFUS over 12 years
- 5,825 deaths from all causes
  - 2,132 from CVD
  - 1,576 from CHD
- Compared to men w/o a hx of gout & CHD @ baseline
  - RR w hx gout: 1.28 Total Mortality
  - 1.38 CVD Deaths
  - 1.55 Fatal CHD
  - RR w hx CHD: 1.25 Total Mortality
  - 1.26 CVD Deaths
  - 1.24 Fatal CHD
- **Men w gout had higher risk of non-fatal MI than w/o gout**

Can Controlling Hyperuricemia & Gout Ameliorate Comorbidities?

• Cause & effect not entirely clear
• Data available are insufficient for proof
• Challenge – adjusting for multiple comorbidities
• Do reveal “trends” – more studies indicated


Can Controlling Hyperuricemia & Gout Ameliorate Comorbidities?

• 5 - yr febuxostat study (1)
• Pts divided into quartiles by urate lowering
• Preservation of eGFR correlated with lowest urate rather than physiologically over time
• Pts w least urate lowering had signif decline in eGFR
• 2 other studies using allopurinol yielded similar results (2, 3)

Adolescent Hypertension & Hyperuricemia

- Pilot study 30 adolescents 11 – 17 yoa with essential HBP & inc SUA
- Allopurinol 200mg bid x 4 wks
- 20/30 with inc sua normalized BP
- 1/30 of controls on placebo


Why is uric acid not always found to be an independent risk factor for CV events?¹

- If UA caused CVD as a consequence of causing HBP or renal dx, then it would not be expected to be independent of these variables when evaluated as risk factors for CV events
- SHEP Trial² – diuretics shown to reduce CV mortality in the elderly
  - Recent sub – analysis
    - Cardioprotection is lost in those pts where SUA levels increased
- Beneficial antioxidant actions of UA may partially counter its potential detrimental effects³

Johnson RJ et al. Hypertension. 2003;41:1183¹
Conclusion

Hyperuricemia & gout should alert the clinician to an overall increased risk of CVD & especially in those patients with other risk factors for CV events

Forman

“I told him it wouldn't kill him to try to be nice once in a while, but I was wrong.”