L’iperuricemia cronica nell’anziano con o senza deposito di urati: cause e trattamento

Epidemiology of gout and hyperuricaemia (SUA > 6 mg/dL) in Italy during the years 2005–2009

Human urate homeostasis

Tophi and Frequent Gout Flares Are Associated With Impairment to Health Related Quality of Life
Prevalence of gout in men in New Zealand (Maori) compared with men of European descent

Associations of purine-rich food groups with gout, from the Health Professionals Follow-up Study (HPFS)

Associations of alcoholic beverages with gout, from the Health Professionals Follow-up Study (HPFS)

Summary of the effects of beer, liquor and wine on SUA or gout by study

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population Notes</th>
<th>Beer</th>
<th>Liquor</th>
<th>Wine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choi, HK et al. 2004;781</td>
<td>Case-control study</td>
<td>499 men</td>
<td><strong>p</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MacFarlane LA et al. 2014;140</td>
<td>Cross-sectional study</td>
<td>1237 men and females</td>
<td></td>
<td><strong>p</strong></td>
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<td><strong>p</strong></td>
</tr>
</tbody>
</table>

SUA: serum urate acid
*Other confounders in analysis
**Other confounders in analysis
Sugar Sweetened Beverages and Serum Uric Acid levels in Adolescents

Vitamin C Intake and Serum Uric Acid Concentration in Men

Age- and sex-adjusted serum uric acid levels according to categories of coffee, tea, and caffeine intake: NHANES-III

Summary of the effects of diet on risk of gout
Dose-Response Association and CVD risk factors with Hyperuricemia

Effects on Uric Acid Metabolism of the Drugs

The therapeutical management of chronic hyperuricemia in the third millennium

- What we would like to treat/prevent by urate lowering treatment?
  - Flares, tophi, nephrolithiasis and … subclinical damage?
  - Cardio-nephro-metabolic protection (?)
- How we can reduce serum uric acid?
  - Lifestyle
  - Drugs
Gout: The Fashionable Disease
"the disease of kings"
"rich man's disease"

Gout in the elderly: (a)typical features

- Gout is one of the most painful type of arthritis
- However, gout in the elderly tend to be more indolent while gout flares tend to be more polyarticular
- Given the chronicity of gout, elderly patients tend to have an increased incidence of tophi, especially of the elbows and hands

Likelyhood ratio for various features in the diagnosis of gout - EULAR

Gout in the Elderly can be mistaken for changes that are usually attributed to OA or RA

The presence of tophi in the hands and the upper extremities can be mistaken for rheumatoid nodules.
Tophi can supervene on Heberden's and Bouchard's nodes.
Musculoskeletal US can be able to visualize intraarticular crystal deposits with a characteristic hyperechoic enhancement of the outer surface of the hyaline cartilage, known as the "double contour sign."

Asymptomatic articular damage in hyperuricemia

- Musculoskeletal US
- Characteristic hyperechoic enhancement
- Double contour sign

Asymptomatic articular damage in hyperuricemia

<table>
<thead>
<tr>
<th>Anatomical site and US findings</th>
<th>Hyperuricemic (n=100 joints)</th>
<th>Nonuricemic (n=100 joints)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Double contour sign</td>
<td>21 (21%)</td>
<td>8 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Joint early widening (crystal/fluid hyperemia)</td>
<td>52 (52%)</td>
<td>25 (25%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Power Doppler signal</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Bone erosion</td>
<td>12 (12%)</td>
<td>8 (8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Knee (n=16)</td>
<td>17 (17%)</td>
<td>8 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Double contour sign</td>
<td>17 (17%)</td>
<td>8 (8%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Knee in NC</td>
<td>27 (27%)</td>
<td>2 (2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Hyperuricemia and gout: time for a new staging system?

- Stage A: Asymptomatic disease
- Stage B: Symptomatic disease
- Stage C: Asymptomatic disease with early signs or symptoms of gout
- Stage D: Symptomatic disease with advanced gout

The therapeutical management of chronic hyperuricemia in the third millennium

- What we would like to treat/prevent by urate lowering treatment?
- Flares, tophi, nephrolithiasis and …
- Subclinical articular damage
- Cardio-nephro-metabolic protection (?)
- How we can reduce serum uric acid?
  - Lifestyle
  - Drugs
Epidemiology of gout and hyperuricaemia (SUA > 6 mg/dL) in Italy during the years 2005–2009

Hyperuricemia and CV disease

Editorial Commentary

Determinants of Hyperuricemia

Determinants of Hyperuricemia

Modified from: Rees F et al. Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2014.32

L’iperuricemia induce lo sviluppo di arteriolosclerosi in modo indipendente dalla pressione arteriosa.

Inflammasome: the missing link between gout and cardio-nephro-metabolic disorders?

The Role of NLR3 inflammasome in gout

Inflammasome: the missing link between gout and cardio-nephro-metabolic disorders?

The Role of NLR3 inflammasome in metabolic disease
Study of Serum Uric Acid and its Correlation with Intelligence Quotient and Other Parameters in Normal Healthy Adults

**Hyperuricemia and Cardiorenal Metabolic Syndrome**

Alexander the great, Darwin, Harvey, Newton, Sydenham, ….

This association cannot be mere co-incidence….

Lessons from comparative physiology: could uric acid represent a physiologic alarm signal gone awry in western society?

- Uric acid having similar structure to that of caffeine and theobromine acts as a cerebral stimulant and thought to be responsible for better development of brain and more intelligence
- Uric acid can increase locomotor activity in rats
- Uric acid increases with emotional or physical stress

Uric Acid and Dementia in Community-Dwelling Older Persons: The InChianti Study

1,016 elderly subjects (age 74.38 ± 7.58 years)

<table>
<thead>
<tr>
<th>Adjusted for</th>
<th>UA tertile</th>
<th>OR</th>
<th>95 CI</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>1) 3.82 ± 0.53 mg/dL</td>
<td>2.34 (0.87–6.24)</td>
<td></td>
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<tr>
<td></td>
<td>2) 5.05 ± 0.27 mg/dL</td>
<td>3.06 (1.10–8.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) 6.72 ± 1.24 mg/dL</td>
<td>3.06 (1.10–8.52)</td>
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<tr>
<td></td>
<td>1) 3.82 ± 0.53 mg/dL</td>
<td>2.62 (0.91–7.52)</td>
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<tr>
<td></td>
<td>2) 5.05 ± 0.27 mg/dL</td>
<td>3.32 (1.06–10.42)</td>
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<tr>
<td></td>
<td>3) 6.72 ± 1.24 mg/dL</td>
<td>3.32 (1.06–10.42)</td>
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<tr>
<td></td>
<td>1) 3.82 ± 0.53 mg/dL</td>
<td>11.02 (1.69–72.00)</td>
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</tr>
<tr>
<td></td>
<td>2) 5.05 ± 0.27 mg/dL</td>
<td>18.89 (2.04–174.67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) 6.72 ± 1.24 mg/dL</td>
<td>18.89 (2.04–174.67)</td>
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Cerebral Ischemia Mediates the Effect of Serum Uric Acid on Cognitive Function

Mean age, 59.9 ± 18.9 mg/dL
Serum UA, 4.5 ± 1.4 mg/dL

<table>
<thead>
<tr>
<th>Serum UA</th>
<th>P</th>
<th>WMH Volume</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.82 mg/dL</td>
<td>0.232</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>5.05 mg/dL</td>
<td>0.001</td>
<td>0.367</td>
<td></td>
</tr>
<tr>
<td>6.72 mg/dL</td>
<td>0.118</td>
<td>0.409</td>
<td></td>
</tr>
</tbody>
</table>

Could uric acid directly promote neuronal dysfunction and/or damage?
The therapeutical management of chronic hyperuricemia in the third millennium

- What we would like to treat/prevent by urate lowering treatment?
  - Flares, tophi, nephrolithiasis and ...
  - Subclinical articular damage
  - Cardio-nephro-metabolic protection (?)
- How we can reduce serum uric acid?
  - Lifestyle
  - Drugs

Patient education and appropriate lifestyle advice (healthy diet and reduced consumption of beverages containing fructose and alcohol, beer especially) are core aspects of management. Strength of recommendation (95% CI): 83 (75, 91)

Charles Dickens wrote about gout in both Bleak House and The Pickwick Papers.

In The Pickwick Papers, the character Sam Weller warns his father that drinking will lead to gout.
The purine degradation pathway

Efficacy and Safety of Febuxostat for Urate Lowering in Gout Patients ≥65 Years of Age

- Allopurinol 200/300 mg (baseline n=131)
- Febuxostat 40 mg (n=115)
- Febuxostat 80 mg (n=120)

- Moderate Renal Impairment
- All subjects

Elderly Subjects Often Have a Great Frequency of Comorbidities and Are Taking Multiple Drugs
Selected concomitant medication use among elderly subjects during the CONFIRMS trial

Febuxostat is an effective alternative to allopurinol which shows greater efficacy and minor adverse effects as urate lowering agent. Starting doses are to be low and increased if necessary. Strength of recommendation (95% CI): 82 (76, 89)

IMPORTANT QUESTIONS

- What threshold should be adopted to define hyperuricemia?
- Is hyperuricemia an independent risk factor for cardiovascular disease?
- Can we improve cardiovascular and renal outcomes by lowering sUA levels?
- When should urate-lowering therapy be started?

Effect of Uric Acid Lowering on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension

Mean 24 hour blood pressure

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Effect of Uric Acid Lowering on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension

Mean 24 hour blood pressure
Comparison of randomized studies using xanthine oxidase inhibition in heart failure

<table>
<thead>
<tr>
<th>Author</th>
<th>Heart Failure Population</th>
<th>Xanthine oxidase inhibitor</th>
<th>Follow-up (years)</th>
<th>Primary Outcomes Defined</th>
<th>Primary outcomes result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Giovani et al. 2015</td>
<td>245 with SCA-7/5</td>
<td>Allopurinol</td>
<td>20</td>
<td>Clinical outcome (major cardiovascular events)</td>
<td>3% improved in both allopurinol and placebo</td>
</tr>
<tr>
<td>Gugli et al. 2005</td>
<td>32 NYHA, III</td>
<td>Allopurinol</td>
<td>4</td>
<td>Major cardiovascular events</td>
<td>No difference in mortality (allopurinol vs placebo)</td>
</tr>
<tr>
<td>Naka et al. 2019</td>
<td>58 NYHA, III</td>
<td>Allopurinol</td>
<td>36</td>
<td>Composite endpoints (death, MI and stroke)</td>
<td>Allopurinol did not improve compared to placebo</td>
</tr>
<tr>
<td>Han et al. 2015</td>
<td>80 NYHA, III</td>
<td>Oxypurinol</td>
<td>28</td>
<td>Major cardiovascular events</td>
<td>5% increased in fatal and non-fatal cardiovascular events in the oxypurinol group</td>
</tr>
<tr>
<td>Gondek et al. 2005</td>
<td>45 NYHA, III</td>
<td>Oxypurinol</td>
<td>5</td>
<td>Major cardiovascular events</td>
<td>No difference in mortality (oxypurinol vs placebo)</td>
</tr>
<tr>
<td>Giovani et al. 2015</td>
<td>58 NYHA, III</td>
<td>Allopurinol</td>
<td>12</td>
<td>Major cardiovascular events</td>
<td>No difference in mortality (allopurinol vs placebo)</td>
</tr>
</tbody>
</table>

HBP: Systolic and diastolic blood pressure, MI: myocardinial infarction, BP: blood pressure

**Reaction scheme for the XO-mediated conversion of hypoxanthine to UA and suicide inhibitor allopurinol to the dead-end inhibitor, oxypurinol**

**Allopurinol inhibits uric acid formation but produces ROS**

**Allopurinol and Cardiovascular Outcomes in Adults With Hypertension**

A total of 2032 allopurinol-exposed patients and 2032 matched nonexposed patients were studied: 10-year period
**Febuxostat: RCT with CV outcome**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drug</th>
<th>Objective</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>BP control</td>
<td>Febuxostat vs. Allopurinol</td>
<td>Clinic and ABPM</td>
<td>NCT01701622</td>
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<tr>
<td>Coronary endothelial dysfunction</td>
<td>Febuxostat vs. Placebo</td>
<td>Coronary flow</td>
<td>NCT01763996</td>
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<tr>
<td>BP control</td>
<td>Febuxostat vs. Placebo</td>
<td>ABPM</td>
<td>NCT01496469</td>
</tr>
<tr>
<td>Exercise tolerance in chronic angina</td>
<td>Febuxostat vs. Placebo</td>
<td>Exercise test (ETT)</td>
<td>NCT01549977</td>
</tr>
</tbody>
</table>

**Total health care resource costs according to SUA levels**

![Total hospitalization costs according to SUA levels](image)

Degli Esposti L et al, NMCD 2014

**2014 EULAR recommendations on the management of gout**

**Recommendation 11: (ULT)**

- All ULT should be started at a low dose and subsequently titrated upwards until the SUA target is reached. SUA below 6 mg/dl (360 µmol/L) should be maintained lifelong.