Hyperurikämie - nur Gicht oder auch kardio-renales Risiko?

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Hyperurikamie - das Zipperlein!
Hyperuricemia & cardio-renal risk

Animal experiments: male Sprague Dawley rats fed 2% oxonic acid (OA) on low salt diet (LS) → mild hyperuricemia → kidney biopsies after 5 weeks: afferent glomerular arterioles

⇒ systemic/intrarenal hypertension & glom. arteriolopathy in hyperuricemic animals, abolished by allopurinol

Rats - hyperuricemia & atherosclerosis

Uric acid in VSMC cultures (rats)

↑ Platelet-derived growth factor (A &C chains)

↑ Tissue Angiotensin II - attenuated by ACE-I & ARBs

↑ Oxidative stress ↓ NO bioavailability

VSMC proliferation / hypertrophy

ATHEROSCLEROSIS

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Hyperuricemia and hypertension

Meta-Analysis:
- 18 prospective cohort studies
- 55’607 subjects
- endpoint: incident hypertension

Hyperuricemia & coronary artery calcification

Cross-sectional retrospective study 2006-2013:
Check-up in 4884 South Koreans, excluded: <20/>80 years, CAD, gout, nephrolithiasis, medications altering S-UA ⇒ 4188 subjects (2559 males, 1629 females)

Multidetector computed tomography
(3 mm slices, reconstruction interval 1.5 mm)
→ coronary artery calcium (CAC) scores
• CAC group 1: CAC score 0 = calcium absent
• CAC group 2: CAC score 1-299
• CAC group 3: CAC score ≥ 300

Multivariate-adjusted associations between S-uric acid and CAC scores
(adjusted for age, sex, diabetes mellitus, hypertension, smoking, sBP, BMI, CRP, Hb, WBC, eGFR, glucose, lipids)

Hyperuricemia and CV disease - allopurinol in hypertensive adolescents

30 adolescents (11-17 yrs.), never-treated stage 1 hypertension, S-uric acid > 356 µmol/l. Randomization: Allopurinol 2 x 200 mg/d vs. placebo 4 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in casual systolic BP, mm Hg</td>
<td>-2.0 (0.3 to -4.3)</td>
<td>-6.9 (-4.5 to -9.3)</td>
<td>.009a</td>
</tr>
<tr>
<td>Change in casual diastolic BP, mm Hg</td>
<td>-2.4 (0.2 to -4.1)</td>
<td>-5.1 (-2.5 to -7.8)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Table 3. Effect of Placebo and Allopurinol on Non-Blood Pressure End Points

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatmenta</th>
<th>Placebo</th>
<th>Allopurinol</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>72 (67-78)</td>
<td>74 (69-80)</td>
<td>75 (69-80)</td>
<td>.87</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>6.4 (5.6-7.1)</td>
<td>6.2 (5.4-7.0)</td>
<td>6.6 (5.9-7.2)</td>
<td>.56</td>
</tr>
<tr>
<td>Systemic vascular resistance index, (dyne s/cm²)/m²</td>
<td>2478 (2223-2731)</td>
<td>2473 (2232-2615)</td>
<td>2136 (2056-2228)</td>
<td>.03b</td>
</tr>
<tr>
<td>Total body water, L</td>
<td>27.8 (26.0-29.7)</td>
<td>28.0 (26.1-30.1)</td>
<td>28.1 (26.0-29.9)</td>
<td>.86</td>
</tr>
<tr>
<td>Plasma renin activity, ng/mL/h</td>
<td>1.9 (1.7-2.2)</td>
<td>2.1 (1.8-2.4)</td>
<td>1.4 (0.8-2.1)</td>
<td>.00b</td>
</tr>
</tbody>
</table>

aPretreatment values were measured prior to first treatment phase.
bExploratory end points.

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Hyperuricemia & CV disease - Allopurinol effects on LV mass & endothelial dysfunction in CKD - RCT

67 elderly patients, CKD stage 3, LV hypertrophy, randomization: allopurinol 300 mg/d vs. placebo on top of other medication (not different between groups), 9 months, 53 finished study (27 A, 26 P). **NO difference in sBP & dBP at 9 months.**

ΔS-UA: Allopurinol 440 to **260 µmol/l**, Placebo 420 to **440 µmol/l** (p < 0.0001)

Uric acid lowering: effects on Renin-Angiotensin-system and ambulatory blood pressure - RCT

Double-blind placebo-controlled trial 2011-2015
• 149 adults, BMI > 25 kg/m², mean serum UA 6.1 mg/dL (363 µmol/l)
• 62% white, male/female 1 : 1
• Excluded: hypertension, CAD, eGFR < 60, malignancy, liver disease
• Randomization: 8 weeks treatment with
  - Placebo (n = 53, 45 completed study)
  - Allopurinol (n = 49, 35 completed study)
  - Probenecid (n = 47, 40 completed study)

Primary endpoints: systemic and kidney-specific RAS-activity
• NO differences between groups despite significant uric acid lowering in both treatment arms vs. placebo
• NO changes in plasma renin and angiotensin II

Secondary endpoints: mean 24h-BP, awake/asleep BP, night dipping
• NO changes, NO differences between groups

Multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease: the ALL-HEART study

Multicentre, controlled, prospective, randomised, open-label blinded end point (PROBE) trial of allopurinol (up to 600 mg daily) versus no treatment in a 1:1 ratio, added to usual care, in 5215 patients aged 60 years and over with ischemic heart disease (Scotland & GB).

The primary outcome is the composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death.

The study is event-driven and results are expected after 2019.

© B. Hess 4/2017 (from Mackenzie IS et al., BMJ Open, 2016 Sep 8;6(9):e013774. doi: 10.1136/bmjopen-2016-013774)
SUMMARY - Hyperuricemia & CV disease

There is clinical evidence that hyperuricemia:

- ... increases BP / induces systemic arterial hypertension in adolescents, but *not in adults* (different pathophysiology?)
- ... is associated with coronary artery calcification
- ... causes vascular hypertrophy / endothelial dysfunction (reduced flow-mediated dilation)
- ... modestly increases left ventricular mass index

Xanthine oxidase inhibition...

- ... is able to reduce blood pressure in *adolescents*
- ... can attenuate endothelial dysfunction in adolescents and adults
- ... is able to reduce LV mass index in elderly adults

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Hyperuricemia & chronic kidney disease - epidemiology

Vienna Health Screening Project, 21’475 healthy volunteers, mean follow-up 7.4 years, 73’015 follow-up examinations, eGFR calculated by MDRD formula

Statistics:
Adjustments for age, gender, waist circumference, mean arterial BP, antihypertensives, blood glucose, blood lipids, baseline eGFR

Primary outcome/results: development of CKD stage 3 (eGFR < 60) in relation to serum uric acid (S-UA) at baseline:
- Normal reference: S-UA < 7.0 mg/dl (< 416 µmol/l) OR 1.00
- Slightly elevated: S-UA 7.0 – 8.9 mg/dl (416-529 µmol/l) OR 1.74
- Elevated: S-UA ≥ 9.0 mg/dl (> 530 µmol/l) OR 3.12

Hyperuricemia & chronic kidney disease (2)
Allopurinol & chronic kidney disease - randomized evidence

Stable clinical condition

Assessed for eligibility (n=135)

- eGFR < 60 ml/min/1.73 m² (MDRD formula)
- Excluded: (n=22)
  - e-GFR ≥ 60 ml/min/1.73m² (MDRD)

Randomized (n=113)

- Allopurinol group (n=57)
  - Discontinued Prematurely (n=6)
    - Dialysis starting (n=1)
    - Lost to follow-up (n=3)
    - Minor adverse events (n=2)
  - Completed study (n=51)

- Control group (n=56)
  - Discontinued Prematurely (n=9)
    - Lost to follow up (n=6)
    - Dialysis starting (n=1)
    - Deaths (n=2)
  - Completed study (n=47)

Allopurinol & chronic kidney disease
- randomized evidence (2)

Renoprotection - allopurinol vs. febuxostat

Literature search
- 49 full-text articles
- 45 excluded (no RCTs, conference papers, no adequate outcome, duplication)

Meta-analysis
- 4 RCTs included
- Endpoints:
  - S-creatinine
  - eGFR
  - Albuminuria
  - S-uric acid

Allopurinol & chronic kidney disease - the „field“ evidence

Retrospective cohort study:
Medicare data 2006-2012 (U.S.), 5% random sample, age > 65 years, newly treated with allopurinol (e.g. filled allopurinol prescription after 183 days without prescription)

Main outcome: 1st occurrence of renal failure (ICD-9) during follow-up

Predictors: allopurinol dose, duration of allopurinol use

Multivariate adjustments:
- age, gender, race, Charlson-Romano comorbidity index
- Medications: β—blockers, ACE inhibitors, statins, diuretics, allopurinol

Cohort characteristics:
- 30’022 allopurinol treatments without history of renal failure (baseline)
- Follow-up: 8314 episodes with incident renal failure, 21’708 without

Allopurinol & chronic kidney disease - the „field“ evidence (2)

KONKLUSIONEN

1. Hyperurikaemie ist nicht einfach Gicht...

2. Evidenz (exp./klin. Studien) für Hyperurikaemie als...
   ...CV Risikofaktor: Endothelschaden/-dysfunktion, VSMC Proliferation, ↑ BD und ↑ Renin bei Adoleszenten, LVH bei älteren Erwachsenen  
   **ABER:** nur kleine Studien, *grosse randomisierte, placebo-kontrollierte Studien fehlen*
   ...renaler Risikofaktor: gute epidemiologische Evidenz, Harnsäure-Effekt durch Hypertonie verstärkt  
   **ABER:** *grosse randomisierte, placebo-kontrollierte Studien fehlen*

3. Harnsäuresenkung mit Xanthinoxidase-Hemmern...
   ...kann CV und renales Risiko senken, unabhängig von andern RF  
   ...zeigt in höheren Dosen und über längere Therapiedauer whs. mehr Benefit, **ABER:** *keine randomisierte, placebo-kontrollierte Studien*