Hyperuricemia and chronic kidney disease

• Uric acid (UA) is the end product of purine metabolism in humans
• Hyperuricemia refers to a serum UA (SUA) level > 7mg/dl (416 μmol/L) in both adult men and women
Urate handling by the kidneys

• More than 90% of all cases of HUA are the result of the impaired renal excretion of uric acid.
• The prevalence of HUA rises in parallel with the GFR decline
• The prevalence of HUA also rises in parallel with dialysis vintage
• Altered uric acid excretion can result from decreased glomerular filtration, decreased tubular secretion, or enhanced tubular reabsorption
• antioxidant at physiological concentrations,

• prooxidant in the hyperuricemic state

• Hyperuricemia has been reported to be associated with various diseases
The Duality of Serum Uric Acid

**Anti-Oxidant**
- Increased in response to oxidative stress
- Endothelial Protection
- Direct correlation with total anti-oxidant capacity; inverse correlation with oxidative stress

**Pro-Oxidant**
- Increases Oxidative Stress
- Increases inflammation and cytokines (via innate response)
- Induces monocyte apoptosis

Causes of hyperuricemia

- **Primary**
  - No recognized cause
  - Hypoxanthine phosphoribosyltransferase deficiency
  - Increased phosphoribosyl pyrophosphatase activity.

- **Secondary**
  - Hereditary fructose intolerance
  - Mieloproliferative disease
  - Linfo proliferative disease
  - Hemolytic anemia
  - Drugs: Low-doses salicylate, diuretics, pyrazinamide, ethambutol, nicotinamide, ethanol
Urate Nephropathy

- Deposits of monosodium urate crystals surrounded by a giant cell inflammatory reaction in the medullary interstitium and pyramids.
- Clinically: silent or cause proteinuria, hypertension and renal insufficiency.
Uric acid nephropathy

- Precipitation in renal tubules and collecting ducts cause obstruction to urine flow.

- Following sudden urate overproduction and marked hyperuricaciduria:
  - Dehydration and acidosis
  - Lymphoma
  - Cytolytic therapy
Role of transporters in the renal proximal tubule on urate handling
Renal Handling of Urate in Disease

- Inhibition of tubular secretion
  - Competitive anions
- Enhanced tubular reabsorption
  - Dehydration, diuretics, insulin resistance
- Modulation of OAT expression
  - Sex hormones, aging, diuretic therapy
- Mechanisms incompletely defined
  - Hypertension, hyperparathyroidism, certain drugs and lead nephropathy
Schematic Representation of Uric Acid Homeostasis

Factors that increase uric acid levels in CKD Patients:
1. Reduced GFR
2. Diuretic use
3. Increased renal vascular resistance
4. Co-existent insulin resistance

High purine/protein diet
Alcohol consumption
High cell turnover

Renal Excretion

Hypoxanthine
Xanthine

Urate

Xanthine Oxidoreductase

Estrogen
Probenecid
Benziodarone
Losartan

NO₂⁻
NO₃⁻

NO

O₂

O₂⁻NAD⁺

NAD⁺

NADH

ONOO⁻
(Oxidative Stress)
Mechanism by which uric acid contributes to the development of renal and non-renal diseases. RAS, renin–angiotensin system
Relationship of HU with disease

Hyperuricemia

? Cause

Hypertension

? Consequence

Chronic Kidney Disease

? Coincidence

Cardiovascular Disease
Interrelationships (HU, CRD, CVD)

Cell

Tissue Hypoxia → Cell Death → Insulin Resistance

PURINE → XO → URIC ACID → HYPERURICEMIA

SMC Proliferation → Vasoconstriction

RAS Activation

COX2 Activation

HYPERTENSION

ENDOTHELIAL DYSFUNCTION & CARDIOVASCULAR DISEASE

RENAL DISEASE PROGRESSION
<table>
<thead>
<tr>
<th>MECHANISM FOR RENAL DISEASE</th>
<th>MECHANISM FOR HYPERTENSION</th>
</tr>
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<tbody>
<tr>
<td>Oxidative Stress</td>
<td>NOS Inhibition</td>
</tr>
<tr>
<td>RAS Activation</td>
<td>Induction of Endothelial Dysfunction</td>
</tr>
<tr>
<td>Renal Arteriolar Disease</td>
<td>RAS Activation</td>
</tr>
<tr>
<td>Macrophage and T cell</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td></td>
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<tr>
<td>Renal Vasoconstriction and</td>
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<tr>
<td>Ischemia</td>
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</table>
The distribution of the proportion of baseline hyperuricemic status across CKD stages
The complex interplay among hyperuricemia, chronic kidney disease (CKD), and cardiovascular (CV) mortality
## Observational Studies in Normal AHU

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al (2009)</td>
<td>177,570 Volunteers</td>
<td>Risk of chronic kidney disease is 2x in the highest quartile of SUA vs lowest quartile of SUA</td>
</tr>
<tr>
<td>Iseki et al (2004)</td>
<td>48,177 Healthy Japanese</td>
<td>HU increased risk of incident ESRD by 3X in males and 10x in females</td>
</tr>
<tr>
<td>Obermayr et al (2008)</td>
<td>21,475 Austrians</td>
<td>Risk of incident CKD was 63% in SUA &gt;9 mg/dl and 26% in SUA 7-9 mg/dl</td>
</tr>
<tr>
<td>Domrongkitchaiporn et al (2005)</td>
<td>3499 Adults</td>
<td>Highest quartile of SUA associated with highest risk of CKD and 2.14x risk of ESRD</td>
</tr>
<tr>
<td>Weiner et al (2008)</td>
<td>13,338</td>
<td>SUA increase by 1mg/dl confers 7-11% increase in the risk for incident CKD</td>
</tr>
</tbody>
</table>

### CONCLUSION

In the general population, higher levels of SUA conferred greater risks for incident CKD and ESRD. The risks appear to affect females more than males.
## Observational Studies in CKD-AHU

<table>
<thead>
<tr>
<th>Author</th>
<th>Subjects</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siu et al (2006)</td>
<td>177 Patients</td>
<td>Higher SUA associated with doubling of Crea &amp; ESRD. No association following adjustment for baseline GFR</td>
</tr>
<tr>
<td>Syrjanen et al (2000)</td>
<td>223 IgA Nephropathy</td>
<td>HU was associated with risk for progressive CKD. Not statistically significant following adjustment for confounders.</td>
</tr>
<tr>
<td>Tang et al (2009)</td>
<td>134 PD patients</td>
<td>HU was associated with faster decline in residual renal function and increased endothelial dysfunction</td>
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<tr>
<td>Park et al (2009)</td>
<td></td>
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<tr>
<td>Madero et al (2009)</td>
<td>838 CKD3-4</td>
<td>No association between SUA and progression of CKD. Each 1 mg/dl increase in SUA correlated with 17% increase in all cause mortality &amp; 16% increase in CV deaths.</td>
</tr>
</tbody>
</table>

## CONCLUSION

In the CKD patient, there appears to be no correlation between CKD progression/ESRD and hyperuricemia. HU was associated with endothelial dysfunction and mortality.
## Intervention Studies in CKD-AHU

<table>
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<tbody>
<tr>
<td>Patients</td>
<td>54 Patients, Crea &gt;120 umol/L, U Prot &gt;0.5 g/24h</td>
<td>113 Patients, eGFR &lt;60ml/min</td>
<td>53 Patients with CKD and LVH</td>
</tr>
<tr>
<td>Intervention</td>
<td>Allop 100-200 mg OD x 12 months</td>
<td>Allop 100 mg OD x 24 months</td>
<td>Allop 300 mg OD x 9 months</td>
</tr>
<tr>
<td>Methodology</td>
<td>Open-Label RCT</td>
<td>Open Label RCT</td>
<td>Double Blind RCT</td>
</tr>
<tr>
<td>Outcome</td>
<td>16% in Allop group vs 46% in the control group reached the combined endpoint</td>
<td>12% in the Allop group had a CV event vs 27% in the control group</td>
<td>Improvement in surrogate markers for endothelial dysfunction</td>
</tr>
</tbody>
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### CONCLUSION
In the CKD patient, treatment with Allopurinol 100-300 mg/d was associated with less progression in CKD and fewer CV events. No impact on BP and proteinuria.
Hyperuricemia in the general population increases the risk for CKD and ESRD.

Hyperuricemia in CKD patients was not associated with progression to ESRD. It was associated with increased risk for cardiovascular events.

Treating Hyperuricemic CKD patients with Allopurinol 100-300 mg/d for 9-24 months preserved renal function and reduced CV Events.