Hyperuricemia in Chronic Kidney Disease

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Outline

• Case presentation
• Etiology of increased uric acid in kidney disease
• Does hyperuricemia accelerate decline of kidney function?
• Does lowering of serum uric acid help?
• Conclusions

Case 1 – true story

• 55 year old Asian-Canadian woman with a history of esophageal reflux and hypertension goes for routine physical
• Medications include amlodipine 5mg and omeprazole 20 mg daily
• BP 135/80, physical exam unremarkable

Case 1 – true story (continued)

• Lab results
  • Hemoglobin 137 g/l
  • Rest of CBC normal
  • Creatinine 76 umol/l
  • Uric acid 490 umol/l

Case 1 – true story (continued)

• Should she be on uric-acid-lowering therapy?

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Case 1 – true story (continued)

• Family doctor calls her back in, and prescribes allopurinol 300 mg/day

• 2 weeks later the patient develops fever, rash, peripheral eosinophilia
• Repeat creatinine 422 umol/l
• White blood cells and white blood cell casts in the urine

Case 1 – true story (continued)

• Allopurinol is stopped
• Prednisone 0.5 mg/kg is given
• Slow improvement in kidney function and symptoms
• Left with baseline creatinine of 101 umol/l

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Uric Acid Metabolism

• End product of purine metabolism in humans
• At normal pH, 98% of uric acid is in the form of monosodium urate
• The balance between production and excretion rates of uric acid determines the plasma concentration
  • Production via breakdown of endogenous and exogenous purines
  • 2/3 of excretion through the kidneys, 1/3 GI tract

Uric Acid Excretion and Kidney Stones

• pH affects solubility of uric acid: acid pH promotes precipitation, especially in the urine
• Acid urine has been found to be a risk factor for uric acid kidney stones
• A major problem for American soldiers in Guam during WWII
Renal Handling of Filtered Uric Acid

- It's complicated
- Uric acid-specific transporters, especially in the proximal nephron
- Freely filtered at the glomerulus, reabsorbed, secreted and reabsorbed again

Factors that Increase Renal Urate Excretion

- Extracellular fluid volume expansion
- High urine flow rates
- Increased renal blood flow
- Estrogens
- Hyperglycemia

Pharmacologic Agents that Increase Renal Urate Excretion and Cause Hypouricemia

- stimulate tubular secretion
  - glycine
- inhibit reabsorption
  - high-dose salicylates
  - probenecid
  - radiocontrast agents
  - high-dose ascorbic acid
  - losartan (but not other ARBs)

Pharmacologic Agents that Decrease Renal Urate Excretion and Cause Hyperuricemia

- Inhibit tubular secretion
  - low-dose salicylates
  - pyrazinamide, ethambutol
  - nicotinic acid
  - ethanol
  - furosemide, bumetanide
- Stimulate reabsorption
  - thiazides, chlorthalidone, metolazone, triamterene, amiloride
  - chronic lead or beryllium intoxication

Hyperuricemia in Chronic Kidney Disease

- very common finding
- kidneys excrete 2/3 of daily uric acid production
- decreased GFR is likely the predominant mechanism of elevated uric acid

Hyperuricemia and CKD

- Early observation that nearly all patients with gout also had glomerulosclerosis and interstitial fibrosis in the kidneys
- Urate crystals were also found in the renal tubules and interstitium
- Coined the term: “gouty nephropathy”

Talbot JH and Terplan KI Medicine (Baltimore) 1960
Gouty Nephropathy Challenged

- Inulin clearance and PAH clearance (measures of GFR and RBF) in a cohort of patients
- No change in these values in patients with uncomplicated gout, even with kidney stones
- “Renal insufficiency when seen in patients with gout usually correlates with coexistence of hypertension, ischemic heart disease, or primary pre-existent renal insufficiency.”

Yu and Berger Am J Med 1982

So Which Comes First? Hyperuricemia or CKD?

The Next Two Decades

- It was assumed that hyperuricemia was the consequence of renal disease, not the cause
- Patients with hyperuricemia and CKD usually had diffuse vascular disease, so the CKD was attributed to the vascular disease (nephrosclerosis)

Uric Acid as a Renal and Vascular Toxin

- Hyperuricemia induces oxidative stress in the kidney
  - Sanchez-Lozada Am J Physiol 2008
- Uric acid increases blood pressure in the rat
  - Mazzali Hypertension 2001
- Uric acid induces phenotypic transition of renal tubular cells to fibrosis-producing cells
  - Ryu Am J Physiol 2013
- Uric acid induces endothelial dysfunction via impairment of nitric oxide synthesis and insulin resistance
  - Choi FASEB J 2014

- Suggested that uric acid was a cause, not just a consequence, of renal disease
- Uric acid could also be a CV toxin
- Cited studies showing that elevated uric acid predated
  - Hypertension
  - Obesity
  - CKD
  - Diabetes

How Could Uric Acid Lead to Hypertension and Vascular Disease?

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Does Hyperuricemia Accelerate Decline of Kidney Function?
• hyperuricemia is associated with de novo development of CKD
• Is it associated with faster decline in function and death in patients who already have CKD?

The CRIC Cohort
• observational cohort study of patients with mild to severe CKD
• designed to investigate risk factors for progression, CV events and death
• enrolled 3,939 men and women 21-74 years old
• eGFR 20-70 ml/min/1.73M2

CRIC and Uric Acid
• Baseline serum uric acid was measured in 3,885 of the 3,939 patients
• Median follow-up of 7.9 years
• 885 participants reached kidney failure

CRIC and Uric Acid
• The association between uric acid concentration and kidney failure was confounded by eGFR
• Strong relationship between serum uric acid and development of kidney failure in CKD 2 or 3a (HR 1.40 for every 1SD increase in uric acid)
• In stage 3b HR 1.13, but not significant
• In stage 4, higher serum uric acid levels were protective! (HR .82)

Srivastava Am J Kidney Dis 2018
CRIC and Uric Acid

- During the follow-up of 7.9 years, 789 participants died
- J-shaped relationship between baseline uric acid and all-cause mortality

Overall Association of Baseline Serum Uric Acid with Kidney Failure or Death

Srivastava Am J Kidney Dis 2018

The Association of Serum Uric Acid and Kidney Failure Depends on CKD Stage

Srivastava Am J Kidney Dis 2018

Association Between Uric Acid Concentration and All-Cause Mortality

Srivastava Am J Kidney Dis 2018

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The RENAAL Trial

- Trial of losartan in patients with Type 2 diabetes
- Although it was prescribed for its ARB effect, it also lowers serum uric acid
- Could any of the positive outcome be the result of decrease in serum uric acid rather than ARB blockade?

Post hoc Analysis of the RENAAL Trial

- 1342 patients
- Losartan lowered serum uric acid compared to the placebo group (-0.16 mg/dl, p=0.031)

Miao Hypertension 2011

A Randomized Controlled Trial of Allopurinol

- 54 patients with hyperuricemia and CKD were randomized to allopurinol or usual therapy
- Baseline creatinine about 1.7 mg/dl (200 umol/l)
- 25% of patients were diabetic
- 1 year followup

Siu Am J Kidney Dis 2006

Endpoint Analysis at One Year

- 113 patients
- eGFR < 60 ml/min
- Patients randomized to allopurinol 100 mg/day or usual therapy
- Baseline serum uric acid about 7.5 mg/dl

Another Randomized Controlled Trial of Allopurinol

- Use of allopurinol was associated with stabilization of GFR compared to control
- Decline in GFR 3.3 ml/min in control group compared to increase of 1.3 ml/min in allopurinol group

My Two Cents

- Remember the bardoxolone trial
- Beware any study in CKD where the GFR improves over time!

And Even More!

- Allopurinol was also associated with a 71% reduction in cardiovascular events and a similar reduction in hospitalizations

Does Allopurinol Improve Vascular Function in CKD?

- Patients with CKD stage 3 and asymptomatic hyperuricemia randomized to allopurinol vs placebo
- 12 week study
- Allopurinol lowered uric acid levels but didn’t change vascular function

Okay – Lots of Small, Single-Centre Studies

- Systematic reviews and meta-analyses should bring clarity to the subject

Systematic Reviews and Meta-Analyses (1)

- English-only studies
- 545 screened, 8 studies met analysis criteria
- 476 patients
- Median followup 11 months (range 4-24 months)
- Only 2 were placebo-controlled
- Dose of allopurinol 100-300 mg/day
Systematic Reviews and Meta-Analyses (1)

- Authors concluded that the study numbers are too small and heterogeneous to make any conclusions about the effect of allopurinol on progression of chronic kidney disease
- Suboptimal methodology
- Insufficient evidence to recommend uric acid-lowering therapy
- Better trials are needed

Bose Nephrol Dial Transplant 2014

Systematic Reviews and Meta-Analyses (2)

- Literature search without language restriction (compare with 1)
- 5497 articles screened
- 19 studies in the qualitative analysis
  - 14 allopurinol, 2 losartan, 1 amlodipine, 1 benzbromorone, 1 rasburicase
- 11 studies for the meta-analysis (> 3 month duration)

Kanji BMC Nephrology 2015

Systematic Reviews and Meta-Analyses (3)

- Treatment of hyperuricemia as a way to prevent
  - gouty arthritis
  - renal disease
  - cardiovascular events
- 1683 papers reviewed
- 3 studies met inclusion criteria (2 to prevent renal disease and 1 to delay progression of CKD)

Vinik J Rheum 2014
Systematic Reviews and Meta-Analyses (3)

• Authors concluded that the available literature is “sparse” and “fraught with limitations”
• “pharmacological treatment of asymptomatic hyperuricemia cannot be recommended at present for the prevention of gouty arthritis, renal disease or CV events”
• Further well-conducted studies are needed

Vinik J Rheum 2014

Trials in Progress or Not Yet Reported

• Uric Acid Lowering to Prevent Kidney Function Loss in Diabetes: The Preventing Early Renal Function Loss (PERL) Allopurinol Study
• Febuxostat versus Placebo Randomized Controlled Trial (FEATHER)
• Controlled Trial of Slowing of Kidney Disease Progression from the Inhibition of Xanthine Oxidase (CKD FIX)
• 113 studies listed in clinicaltrials.gov

So What do We Know?

• Hyperuricemia as a risk factor for CV events or renal decline is markedly confounded by kidney impairment
• Studies in the last decade suggest that uric acid may be pro-inflammatory and toxic to blood vessels
• There is therefore a physiologic rationale to treat asymptomatic hyperuricemia in the at-risk patient
• To date, however, there is little good evidence to support this practice

The Future

• Hopefully the 113 trials underway will give us guidance as to the validity of treating asymptomatic hyperuricemia