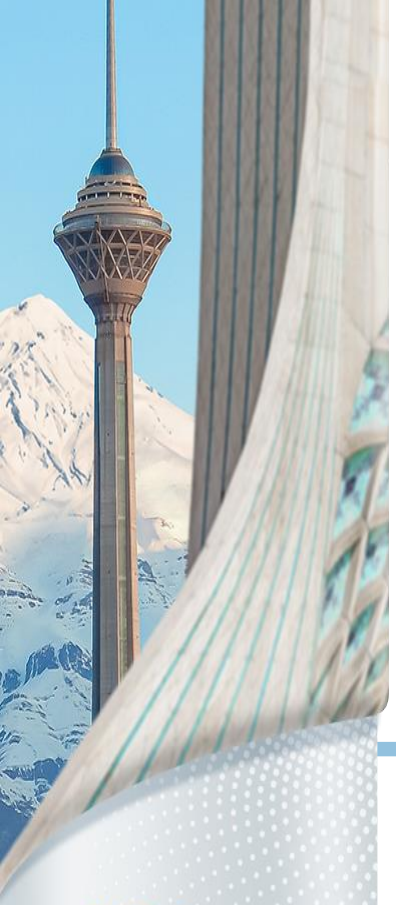
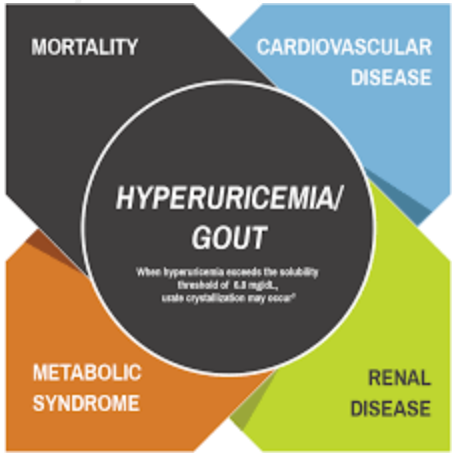
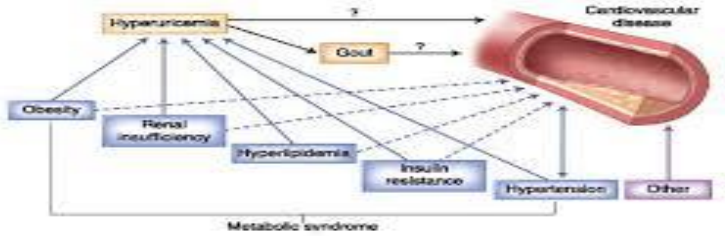


Hyperuricemia and chronic kidney disease: to treat or not to treat

Dr.F.Ahmadi
Professor Of Nephrology
Tehran University Of Medical Sciences



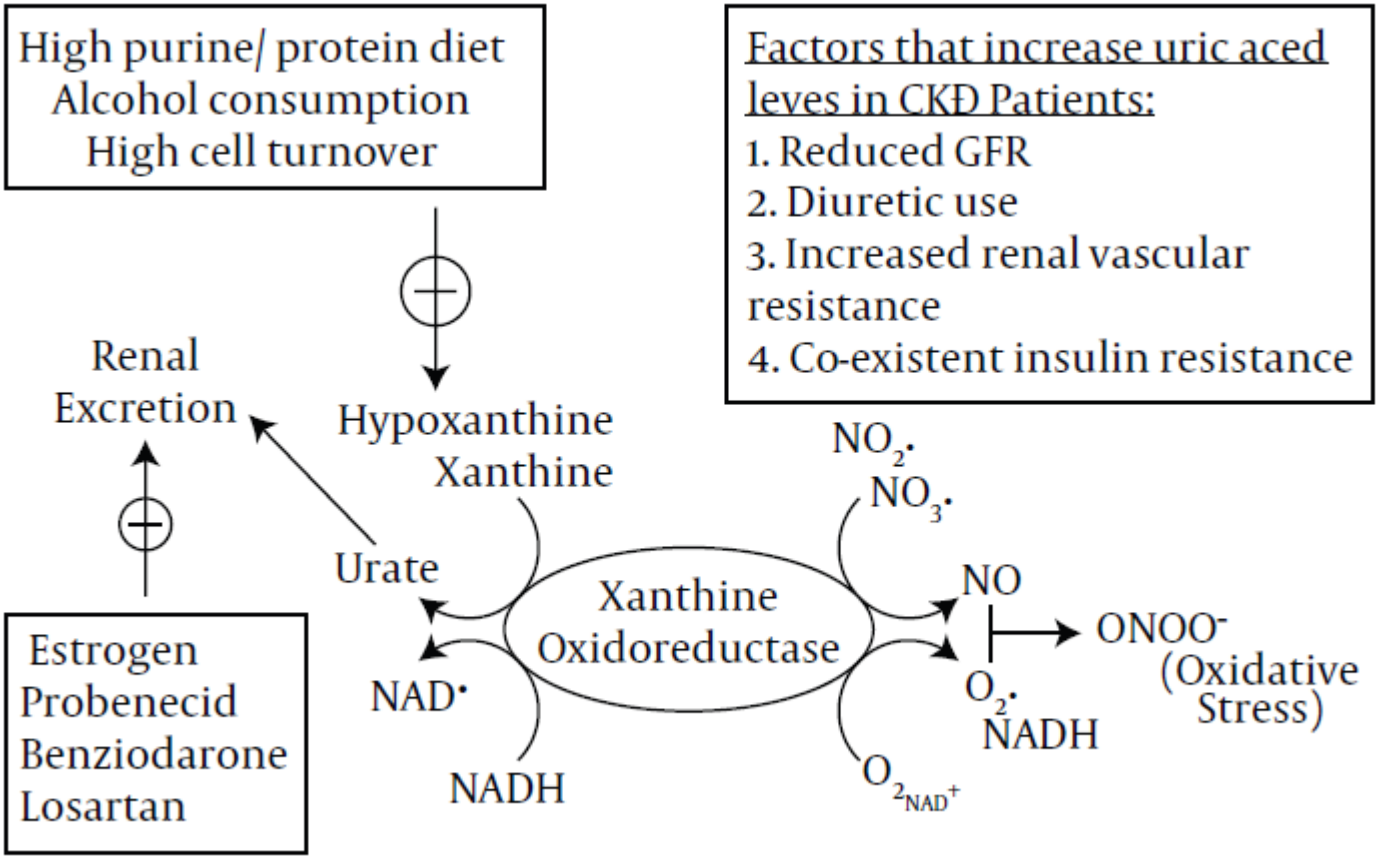


- ✓Hyperuricemia is common in chronic kidney disease (CKD) and may be present in 50% of patients presenting for dialysis.
- ✓The prevalence of chronic kidney disease(CKD) and hyperuricemia is increasing worldwide
- ✓Gout and hyperuricemia are present in 25% and 60% of patients with chronic kidney disease (CKD),respectively
- ✓Hyperuricemia independently predicts new onset CKD

- ✓Hyperuricemia (defined as a serum uric acid level>7 mg/dl in males and >6 mg/dl in women) is common in CKD
- ✓The prevalence of asymptomatic hyperuricemia has been increasing over the past decades, and can be as high as 20–25% in adult males
- ✓Gout has been associated with a higher risk of advanced CKD compared to asymptomatic hyperuricemia

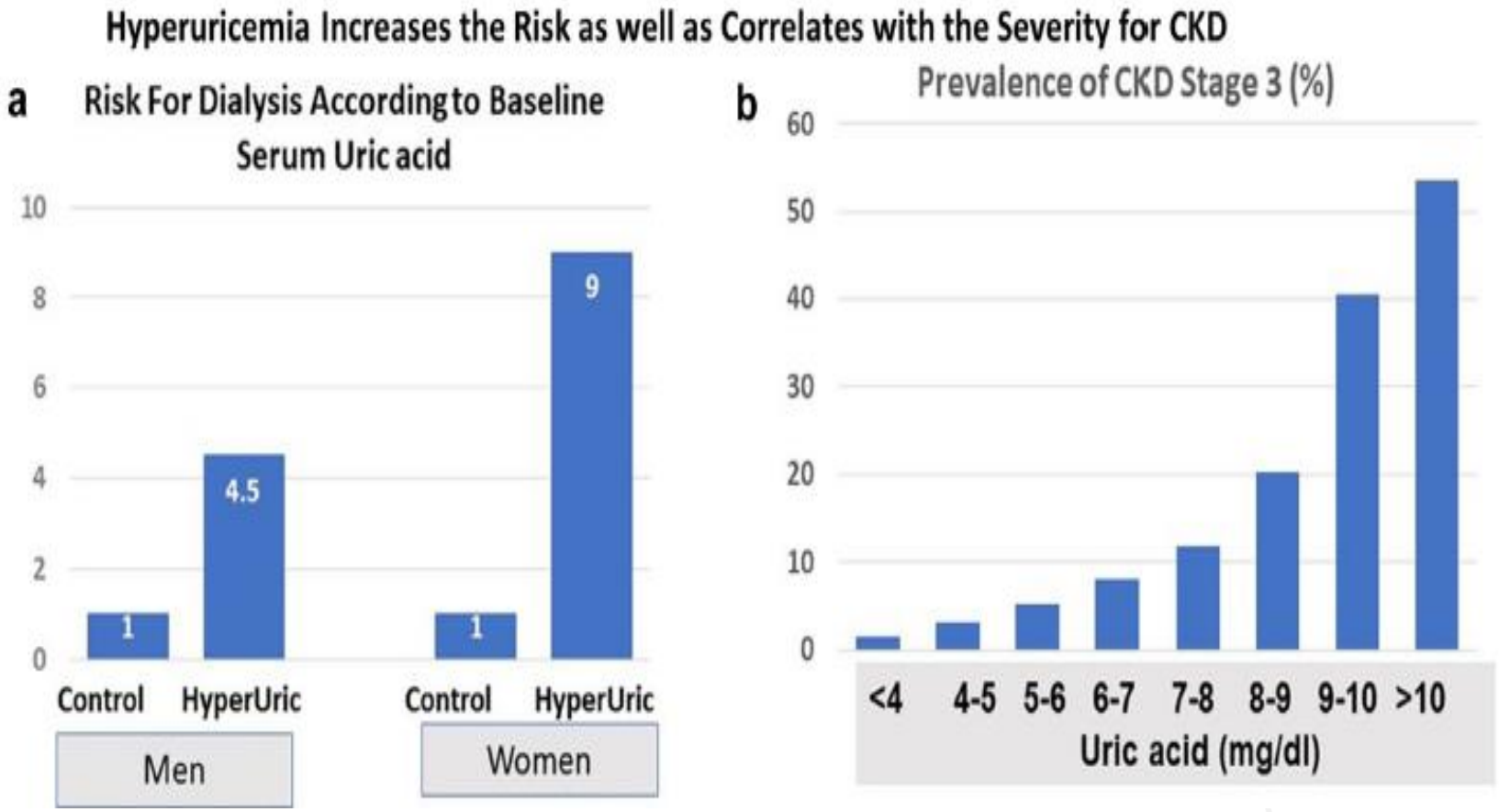
- ✓Today, there remains controversy over the role of uric acid in CKD and cardiometabolic outcomes. Several groups have suggested that asymptomatic hyperuricemia in CKD is benign and should not be treated, or may even be beneficial

Schematic Representation of Uric Acid Homeostasis



Nephro Urol Mon. 2015;7(3):e27233

Relationship of Serum Uric acid with CKD



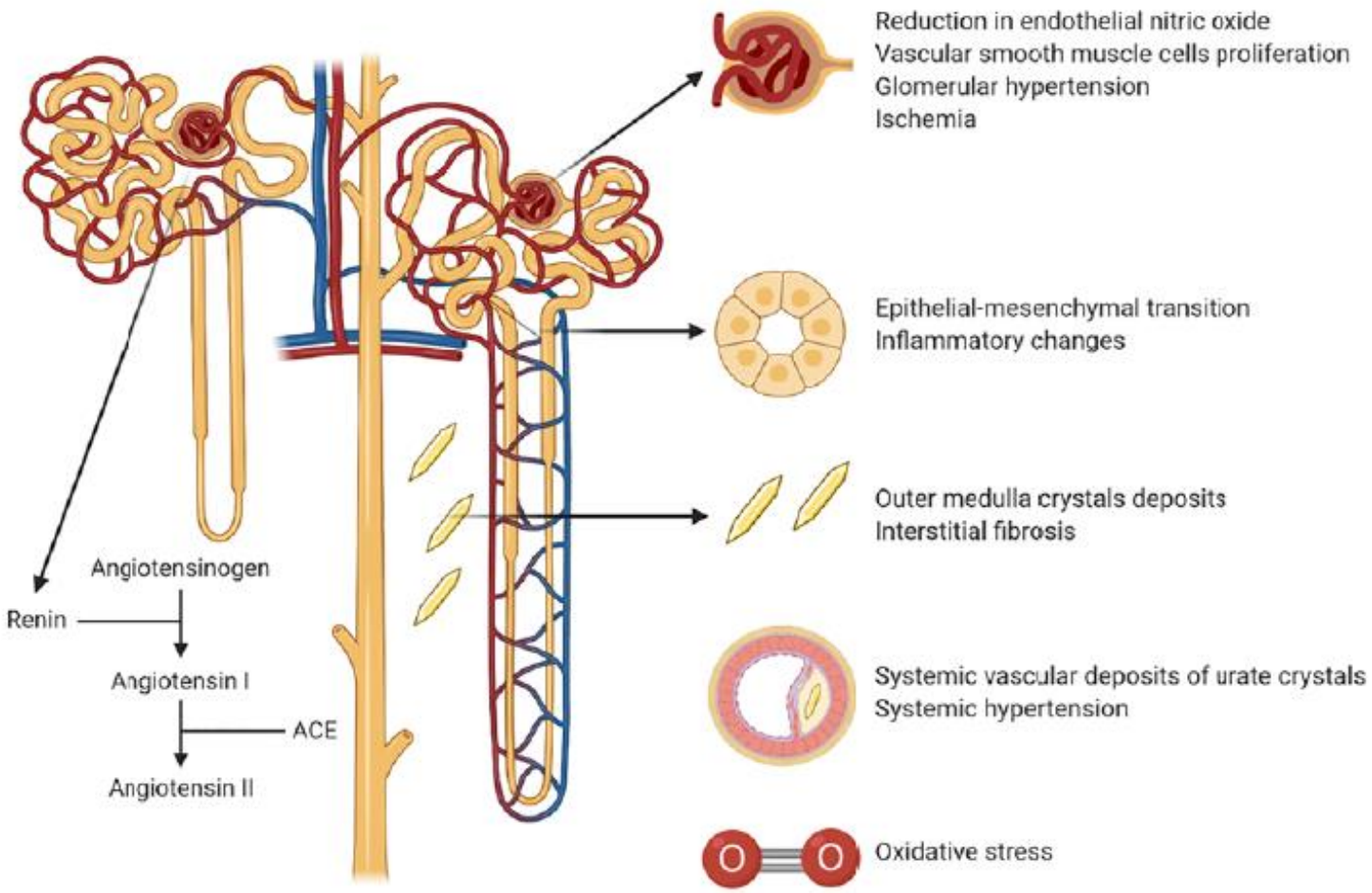
Kidney International Reports (2023) 8, 229–239

Uric acid may be more Important in the Initiation of Metabolic Diseases Rather than the Maintenance

Condition	Initiation	Maintenance
Hypertension	Uric acid-dependent Oxidative stress, Reduced NO, Activated RAS, No kidney damage	Autoimmune inflammation in kidney maintains renal vasoconstriction
Obesity	Uric acid-dependent decrease in mitochondrial function, inhibit AMPK, less ATP generation	Loss of mitochondria resets weight to higher level
Diabetes	Uric acid-induced Insulin Resistance, gluconeogenesis, reduced Insulin secretion	Chronic Islet Injury Leads to Diabetic state in setting of persistent Insulin Resistance
CKD	Uric acid-dependent Glomerular hypertension, vasoconstriction, endothelial dysfunction, inflammation	Chronic Kidney Injury leads to persistent hyperfiltration and glomerular hypertension independent of uric acid levels

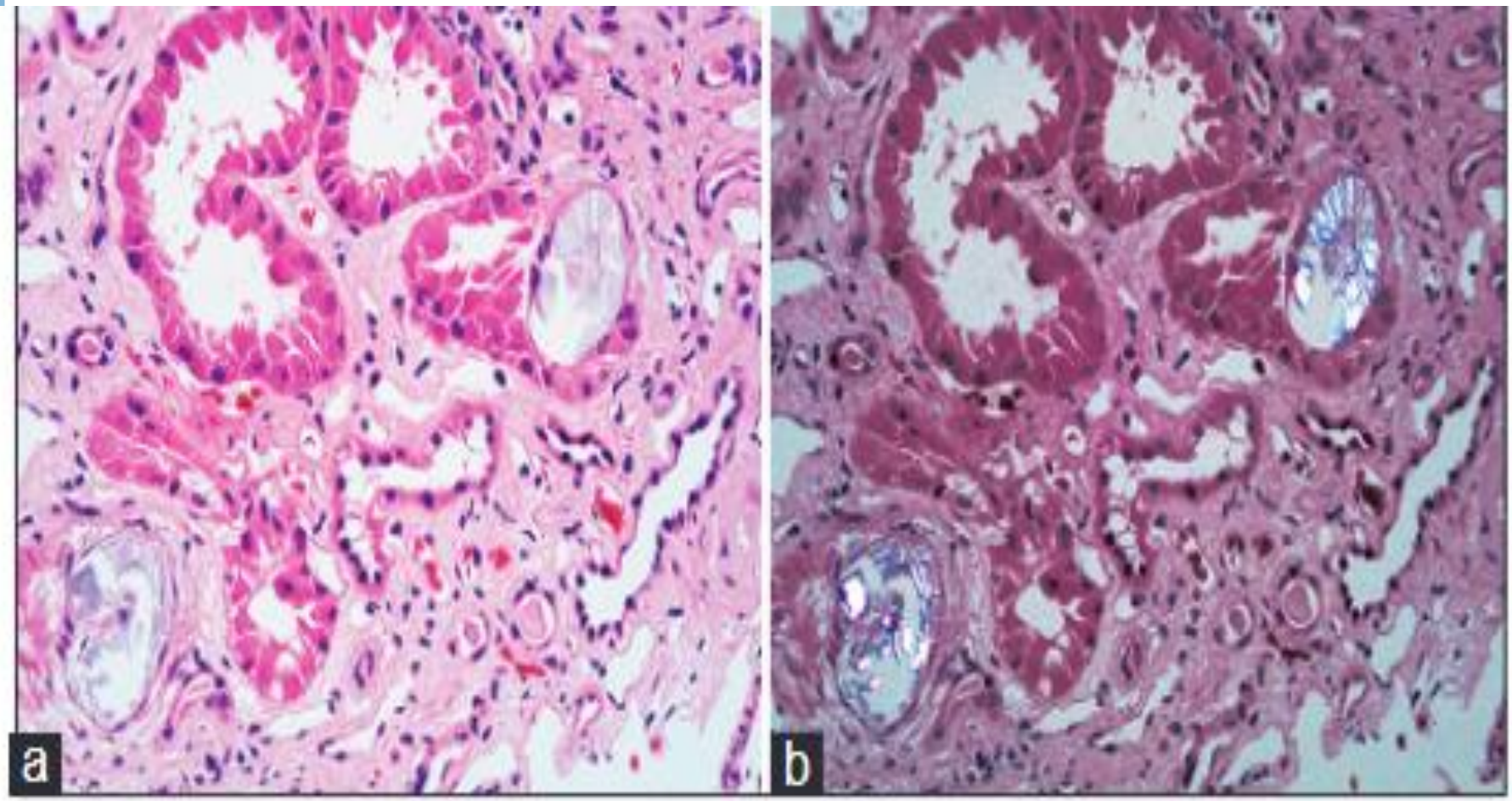
Kidney International Reports (2023) 8, 229–239

Mechanisms of uric acid-induced kidney injury

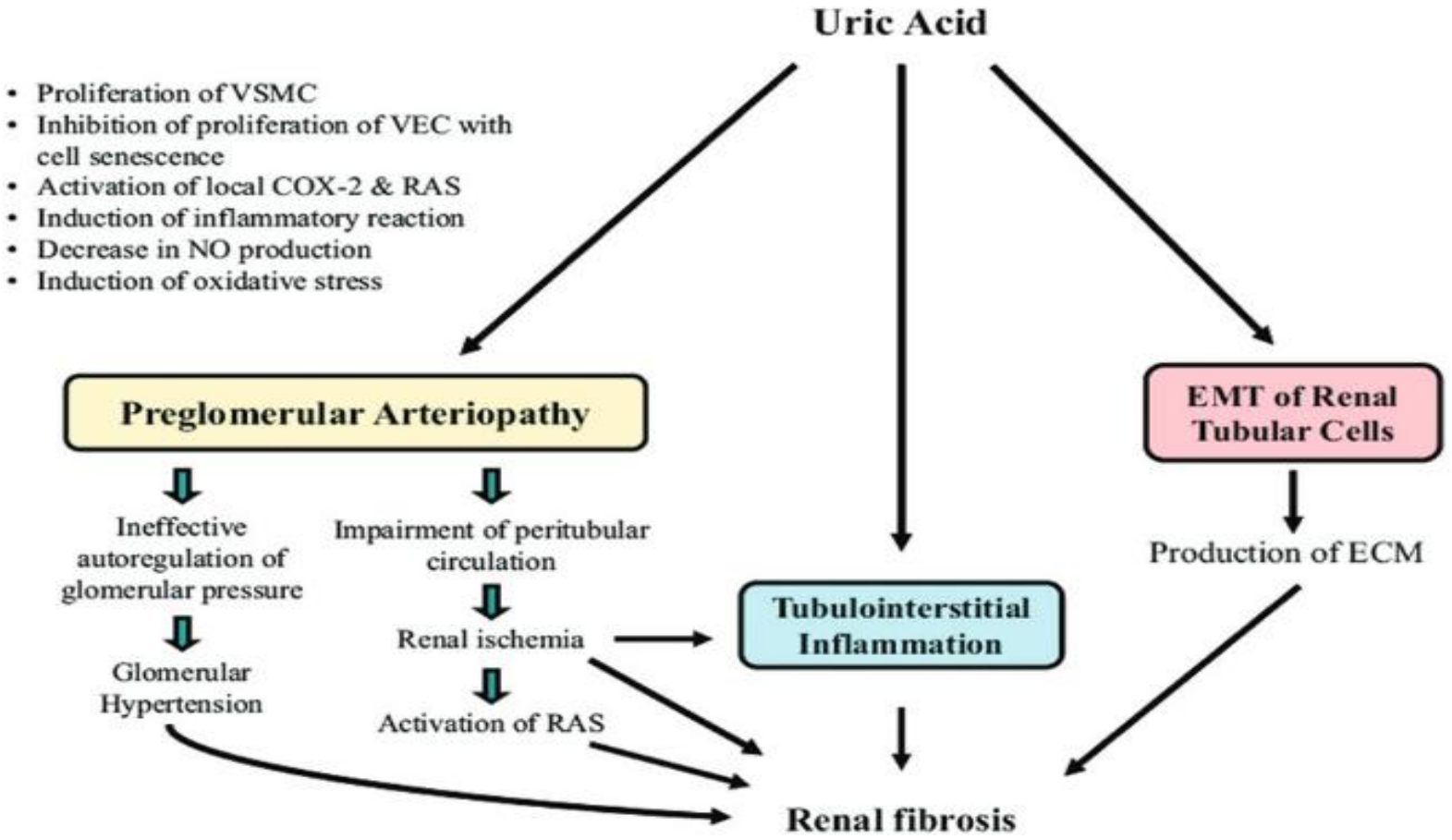


Braz. J. Nephrol. (J. Bras. Nefrol.) 2021;43(4):572-579

Histopathological findings on chronic uric acid nephropathy. (a) Fragments of uric acid crystals in atrophic tubules; (b) clearer crystal image with polarized lighting

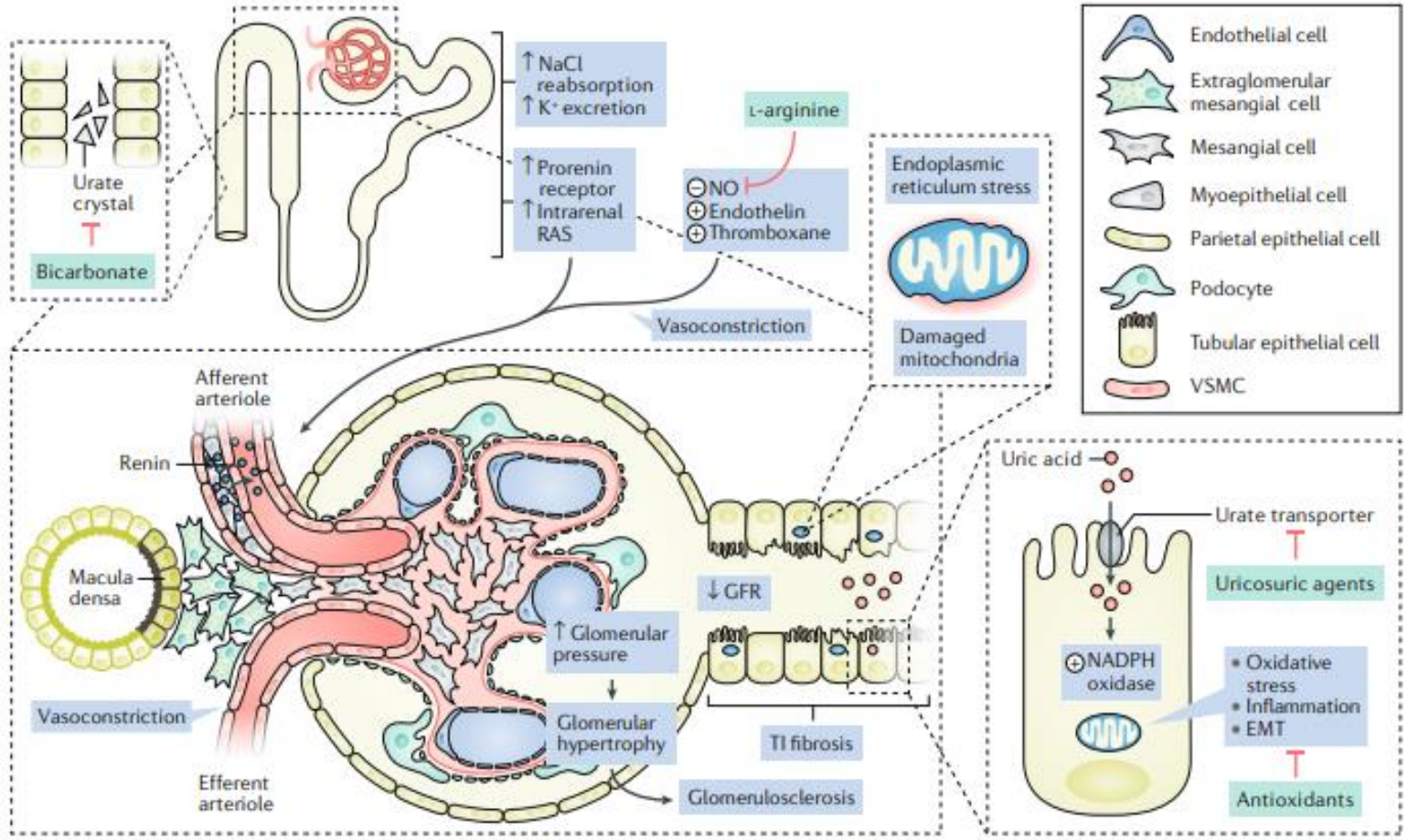


Molecular mechanism of uric acid in conjunction with chronic kidney disease



Open 2021 Oct 14; 9(F):428-435.

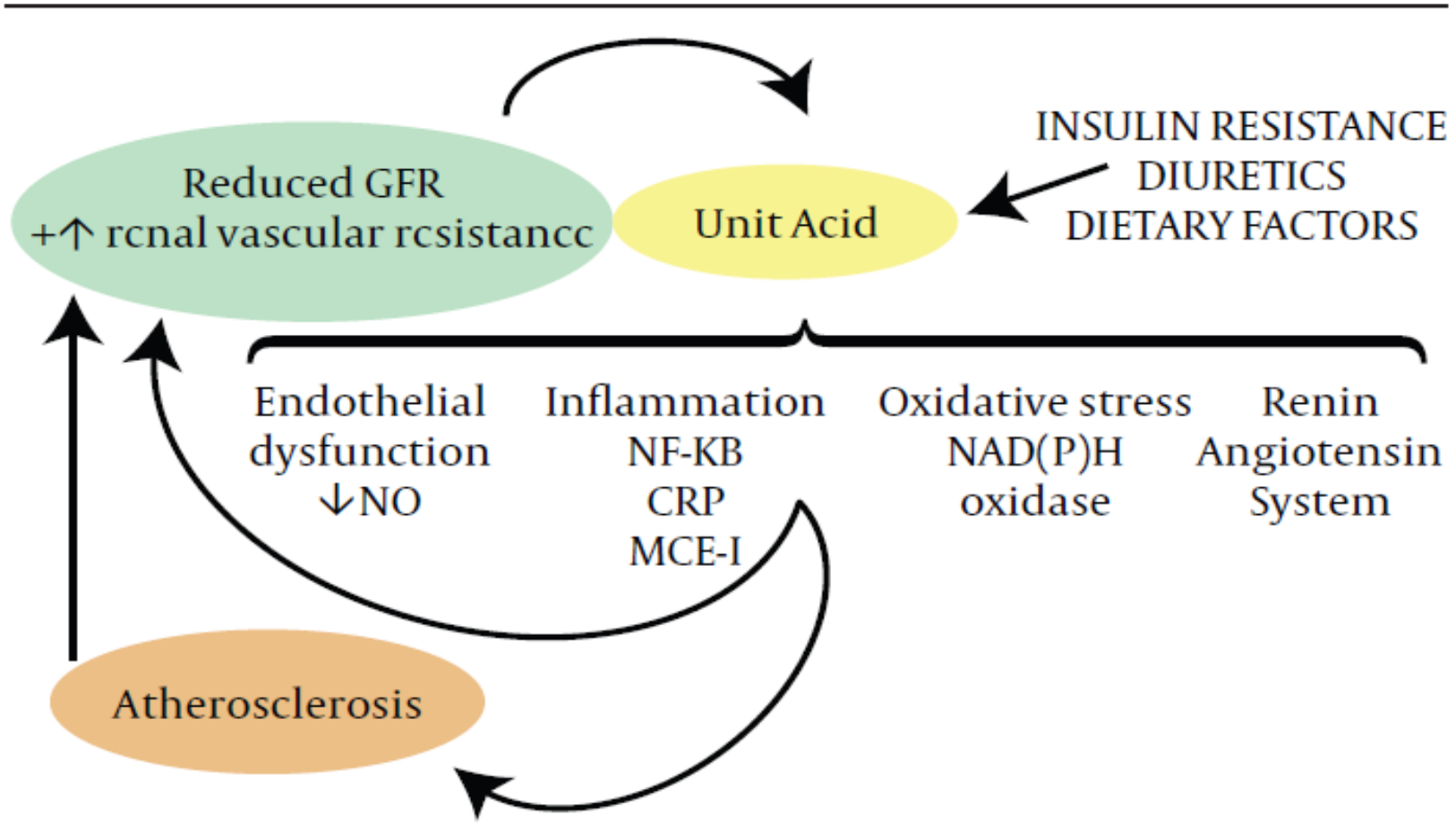
effects of uric acid on the kidney.



Nature Reviews Nephrology
volume 15, pages 767–775 (2019

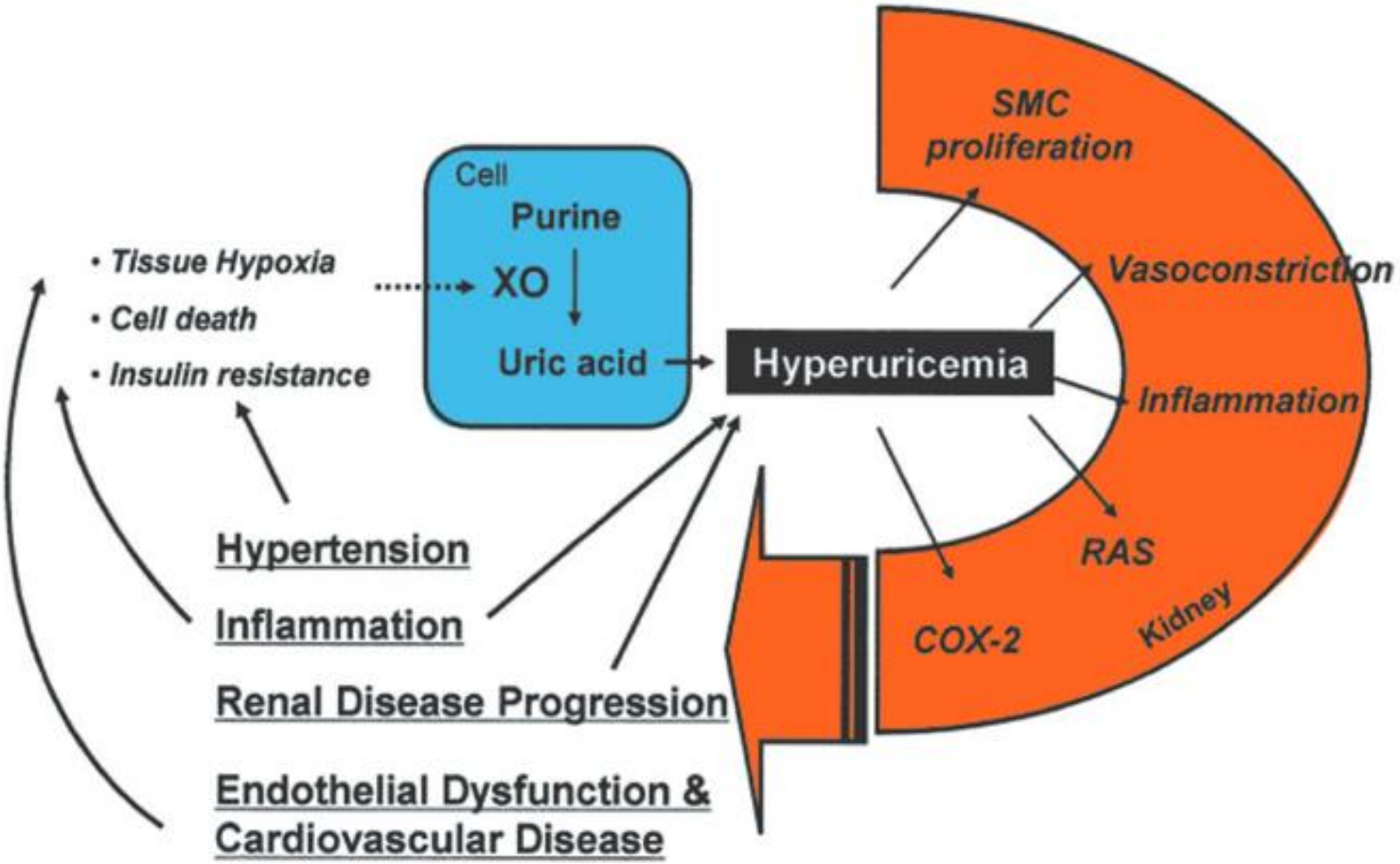
Putative Mechanisms by Which Elevated Serum Uric Acid Levels May Contribute to Chronic Kidney Disease

Development and Progression



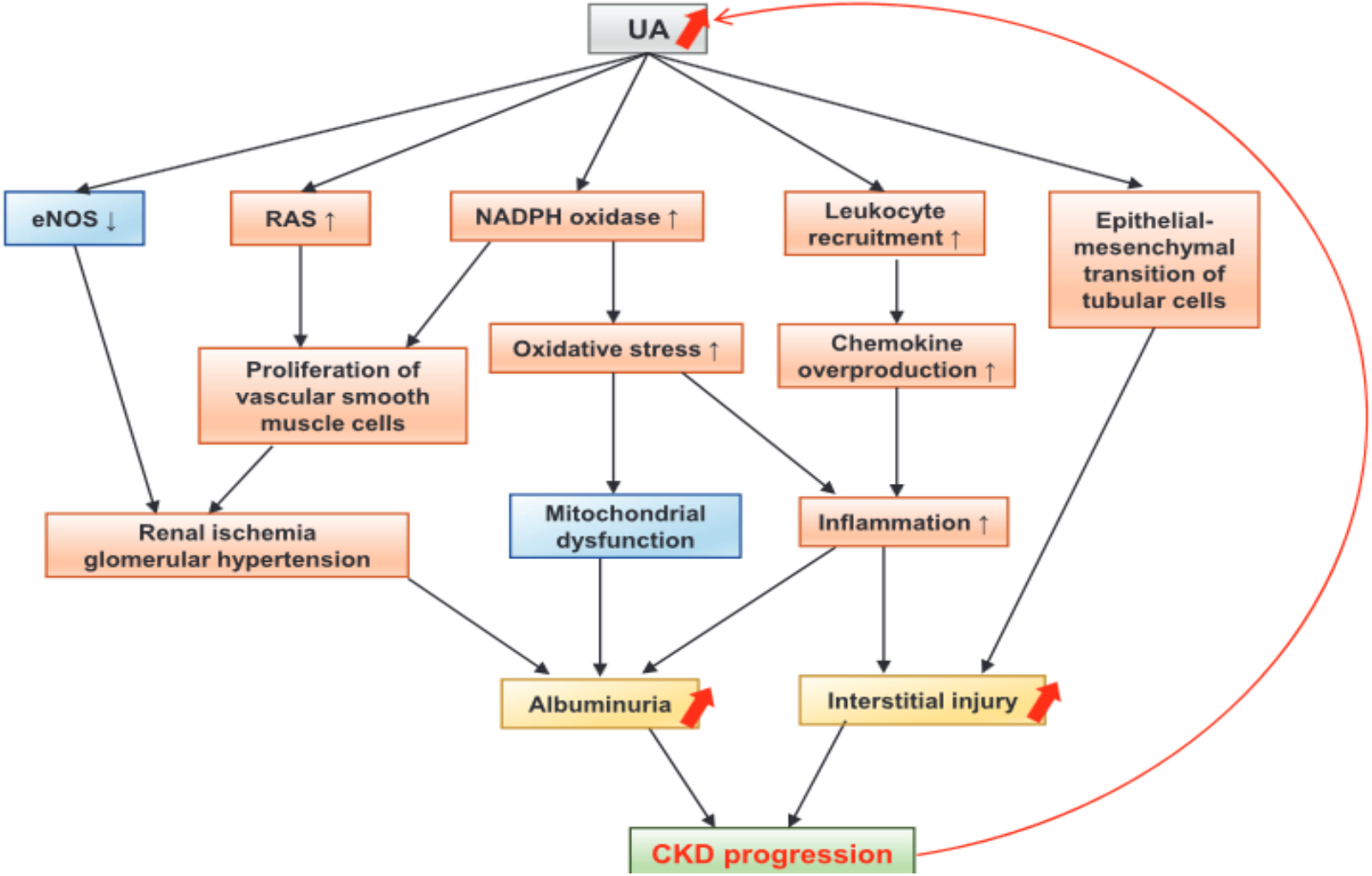
Nephro Urol Mon. 2015;7(3):e27233

The reciprocal relationship between hyperuricemia, hypertension, and chronic kidney disease progressivity



Maced J Med Sci. 2021 Oct 14; 9(F):428-435

Effects of uric acid on the kidney



Hypertension Research (2023) 46:1447–1449

Treatment recommendations

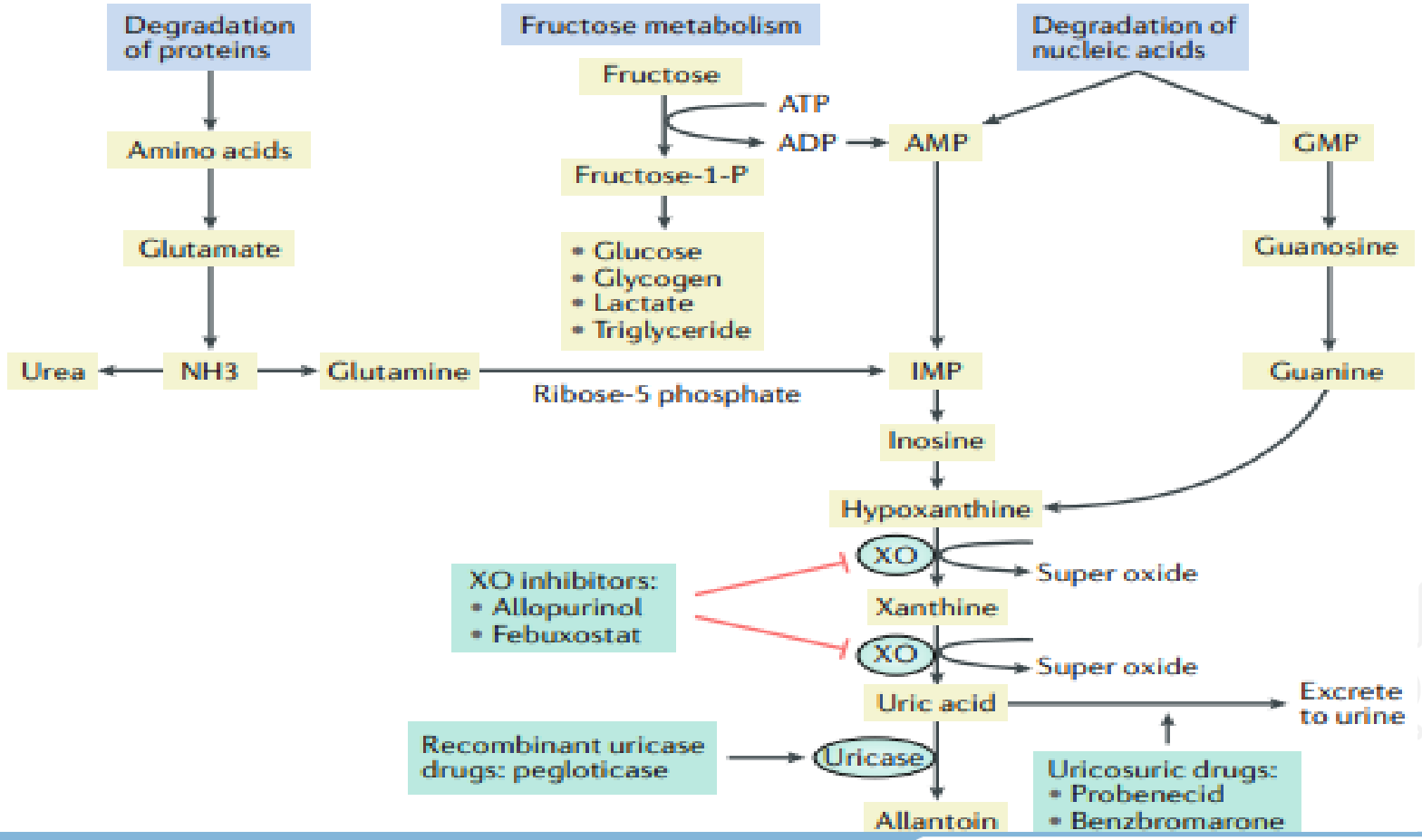
- ✓Allopurinol :severe hypersensitivity syndrome

mimicking a Stevens Johnson syndrome in individuals carrying the HLA B58 allel, might be associated with a higher risk of nephrotoxicity in patients with hyperuricaemia and CKD than in those without CKD

- ✓Febuxostat,: increased all-cause an cardiovascular mortality compared to allopurinol in the CARES trial
- ✓Uricosurics: not recommended in patients with CKD
- ✓Recombinant uricases such as pegloticase

and rasburicase

purine nucleotide degradation and fructose metabolism generate uric acid



Nature Reviews Nephrology
volume 15, pages 767–775 (2019

PERL Study: Can use of allopurinol to lower serum urate level prevent early loss of kidney function in type 1 diabetes?

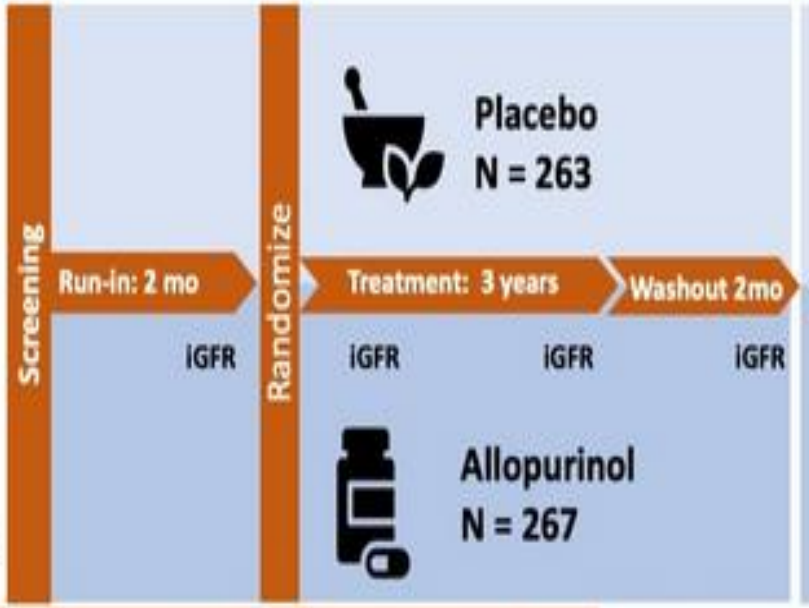
#NephJC

Cohort N=530

- Male 66.2 %
- Age 51 ± 11
- Urate 6.1 ± 1.5
- HbA1c 8 ± 1.3
- Iothalamate GFR (iGFR) 68 ± 17
- UAER 41.6 µg/min

Study Design

Randomized, double blind, placebo- controlled, parallel group, multicenter study at 16 sites



Outcomes

	Urate mg/dl	iGFR ml/min/1.73m²	UAER µg/min
Placebo N = 263	6.1	61.2 (58.1- 64.2)	37.4 (25.3- 55.5)
Allopurinol N = 267	3.8	61.2 (58.1- 64.2)	47.9 (32.5-70.6)

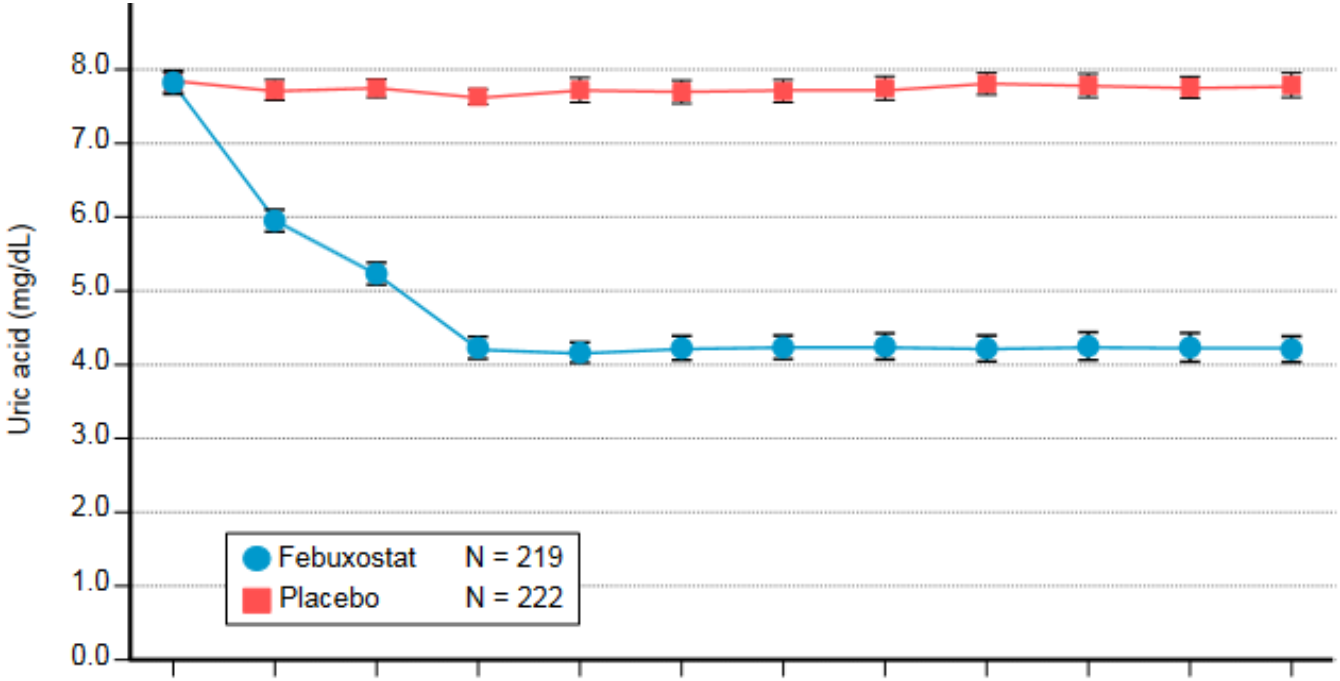
Summary: There was no evidence of clinically meaningful benefits of serum urate reduction with allopurinol in kidney outcomes in patients with type 1 diabetes and early to moderate diabetic kidney disease.

Reference: Doria and Mauer et al. PERL Study Group. Serum urate lowering with allopurinol and kidney function in Type 1 Diabetes. NEJM June 2020; 382 (26)

Visual Abstract by @docanjuyadav

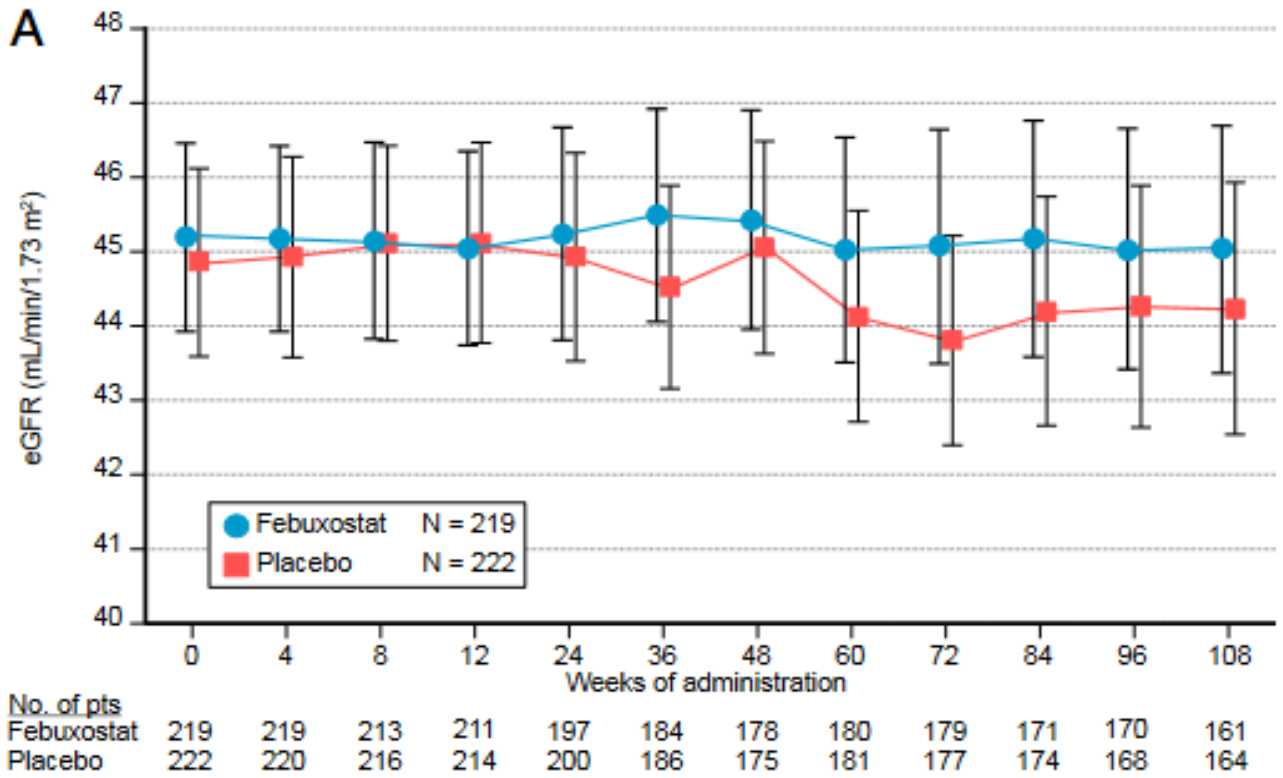
Febuxostat Therapy for Patients With Stage 3 CKD and Asymptomatic Hyperuricemia: A Randomized Trial

Kenjiro Kimura, Tatsuo Hosoya, Shunya Uchida, Masaaki Inaba, Hirofumi Makino, Shoichi Maruyama, Sadayoshi Ito, Tetsuya Yamamoto, Yasuhiko Tomino, Iwao Ohno, Yugo Shibagaki, Satoshi Iimuro, Naohiko Imai, Masanari Kuwabara, Hiroshi Hayakawa, Hiroshi Ohtsu, and Yasuo Ohashi; on behalf of the FEATHER Study Investigators



No. of pts											
Febuxostat	219	219	213	211	197	184	178	180	179	171	170	161
Placebo	222	220	216	214	200	186	175	181	177	174	168	164

Time-course changes in estimated glomerular filtration rates (eGFRs) from week 0 through week 108 of treatment(FEATHER)



AJKD Vol 72 | Iss 6 | December 2018

Systematic Review and Meta-Analysis

Medicine

OPEN

Effects of febuxostat on renal function in patients with chronic kidney disease

A systematic review and meta-analysis

Tsu-Chen Lin, MD[a], Lie Yee Hung, MD[b], Ying-Chun Chen, BS Pharm[c], Wei-Cheng Lo, PhD[d], Chun Hung Lin, MD[e], Ka-Wai Tam, MD[f,g,h,i,j], Mei-Yi Wu, MD[b,d,j,k,l,*]

- ✓The meta-analysis showed that other than its urate-lowering effect, febuxostat presented a reno-protective effect in CKD patients. More studies with larger sample sizes and higher quality are required to clarify the role of febuxostat use in the progression of CKD

Lin et al. Medi cine (2019) 98:29

Effectiveness of Drug Treatments for Lowering Uric Acid on Renal Function in Patients With Chronic Kidney Disease and Hyperuricemia

- ✓Febuxostat shows a tendency to be superior to allopurinol on lowering the decline of eGFR and increment of proteinturia, but the difference does not reach a statistical significance. Regarding its urate-lowering effect, febuxostat appears to be a satisfactory alternative to allopurinol and benzbromarone, and can control blood pressure better.

Uric Acid Lowering and Biomarkers of Kidney Damage in CKD Stage 3

Kidney Medicine

Methods

The 'Parent' Study

Randomized Controlled Trial

N = 80

Intervention

STAGE 3

Hyperuricemia

Allopurinol

12 Weeks

Placebo

Results

- **Serum uric acid** ↓
- **CKD-EPI eGFR** ↔
- **Cystatin C- eGFR** ↔
- **Urine ACR** ↔
- **Urine NGAL** ↔
- **Urine KIM-1** ↔
- **Urine TGF-β1** ↔

Conclusion: Allopurinol lowers serum uric acid in patients with CKD but does not improve markers of kidney function or

Reference: Perrenoud L, Kruse NT, Andrews E et al. Uric acid lowering and biomarkers of kidney damage in CKD stage 3: a post-hoc analysis of a randomized clinical trial. *Kidney Medicine* 2020

Clinical studies on uric acid lowering drugs in patients with CKD

Study	n	Study population	Drug	FU	Result
Siu 2006[67]	54	Patients with hyperuricemia and CKD	Allopurinol	12m	Allopurinol helps preserve kidney function during 12 months of therapy compared with controls
Goicoechea 2010[68]	113	Patients with CKD	Allopurinol vs Controls	24m	Allopurinol decreased C-reactive protein and delayed the progression of renal impairment in patients with chronic kidney disease
Hosoya 2014[69]	123	Patients aged 20–75 years, with hyperuricemia and CKD stages 2-3	Topiroxostat vs Placebo	5.5m	Changes in eGFR were not significantly different between topiroxostat and placebo groups
Sircar 2015[70]	93	Patients with CKD stages 3-4	Febuxostat vs Placebo	6m	Febuxostat significantly decrease the decline in eGFR compared to placebo
Xuemei Liu 2018[71]	832	Meta-analysis: 12 RCTs	Allopurinol or Febuxostat	4-24m	The risk of worsening of kidney function or ESRD or death was significantly decreased in the treatment group compared to the control group
Kimura 2018[72]	443	Japanese patients with stage 3 CKD and asymptomatic hyperuricemia	Febuxostat vs placebo	27m	Febuxostat did not mitigate the decline in kidney function
Lee 2019[73]	141	Patients with hyperuricemia and CKD stage 3	Febuxostat vs Allopurinol	5y	Febuxostat reduced serum uric acid level and delayed CKD progression more effectively than allopurinol

Clinical studies on uric acid lowering drugs in patients with CKD

Badve 2020[60]	363	Patients with stage 3-4 CKD and no history of gout who had a urinary albumin:creatinine ratio≥265 or an eGFR decrease of at least 3.0 mL/min/1.73 m2 in the preceding year	Allopurinol vs Placebo	26m	Allopurinol did not significantly slow the decline in eGFR compared with placebo
Doria 2020[59]	530	Patients with type 1 diabetes, SUA>4.5mg/dL, and eGFR40~99mL/min/1.73 m2	Allopurinol vs Placebo	38m	No significant differences in CKD progression between allopurinol and placebo were observed
Hsu 2020[74]	6057	Patients with stage 5 CKD prescribed either febuxostat or allopurinol	Febuxostat vs Allopurinol	4y	Febuxostat decreased the rate of progression to dialysis
Sezai 2020[75]	55	Patients with CKD stage 3-4	Febuxostat vs Topiroxostat	1y	Febuxostat had stronger renoprotective and antioxidant effects than topiroxostat

Examples of potential clinical trials to investigate the role of uric acid in cardio-renal diseases

Study	Comparison	Outcome	Stratification and Duration
Gout with DECT positive urate crystals in vasculature	Pegloticase vs High Dose Xanthine Oxidase Inhibitor vs Standard of Care	Cardiovascular Events, Vascular Calcification, Renal progression	2 years No restriction on baseline kidney function
Gout with uric acid levels > 7mg/dl despite standard of care	High Dose Xanthine oxidase therapy vs pegloticase vs standard of care	Renal progression, CV events, Vascular events and calcification	2 years No restriction on baseline kidney function
Hyperuricemia with type 2 diabetes or metabolic syndrome (perhaps elevated plasma XO activity)	Xanthine oxidase inhibitor versus placebo	Kidney progression, CV events, metabolic outcomes	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia with Kidney Stones, Hyperuricosuria, or ABCG2 polymorphisms	Xanthine oxidase inhibitor vs placebo vs bicarbonate therapy	Progression of Kidney disease, kidney stones	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia and polycystic kidney disease	Xanthine oxidase inhibitor vs placebo	Renal progression, use of BP medications	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)
Hyperuricemia with elevation of CRP and endothelial dysfunction	Xanthine oxidase inhibitor vs pegloticase vs placebo	CV events, progression of kidney disease	2 years Ideally stratify by kidney function (> 60 vs <60 ml/min/1.73m2)

Kidney International Reports (2023) 8, 229–239

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REVIEW

Uric Acid and Chronic Kidney Disease: Still More to Do

Richard J. Johnson[1], Laura G. Sanchez Lozada[2], Miguel A. Lanaspa[1], Federica Piani[3] and Claudio Borghi[3]

- ✓We suggest that there may be some specific subgroups of subjects with asymptomatic hyperuricemia that would benefit, including those with documented crystal deposition in joints, blood vessels, and the kidneys; those with documented recurrent urate crystalluria or with kidney stones; and those who have evidence for elevated liver or kidney uric acid levels

- ✓We suggest that treatment should be considered for individuals with serum uric acid concentrations of 8 mg/dL or higher and evidence of progression of their kidney disease, as well as patients with a history of gout irrespective of their underlying serum uric acid concentration