ACIDO URICO, HIPERTENSION ARTERIAL y SINDROME METABOLICO: NUEVA ASOCIACION ?

DR. SALVADOR MAGAÑA MERCADO
MEDICINA INTERNA-NEFROLOGIA

AGENDA

BIOQUIMICA Y METABOLISMO DEL ACIDO URICO

FISIOPATOLOGIA DEL DAÑO POR ACIDO URICO

ACIDO URICO Y ENFERMEDAD CARDIOVASCULAR

SINDROME METABOLICO Y ACIDO URICO

TRATAMIENTO

NUCLEOTIDOS Y NUCLEOSIDOS

PURINAS

- ADENINA
- GUANINA

DNA, RNA

- HIPOXANTINA
- XANTINA

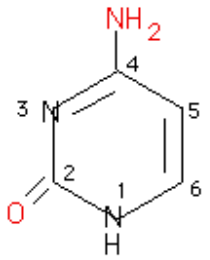
PIRIMIDINAS

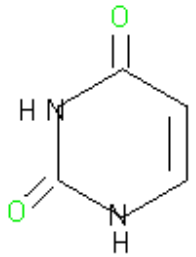
- URACILO → RNA
- TIMINA → DNA
- CITOSINA → DNA, RNA
- AC. OROTICO

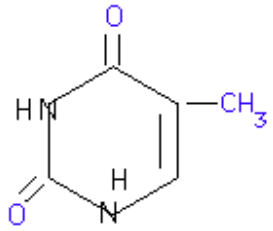
CARBOHIDRATO (RIBOSA, DESOXIRRIBOSA) + BASE NITROGENADA = NUCLEOSIDO

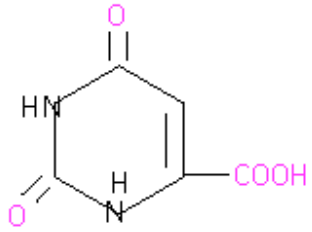
NUCLEOSIDO + FOSFORO INORGANICO (Pi) = NUCLEOTIDO

PIRIMIDINAS

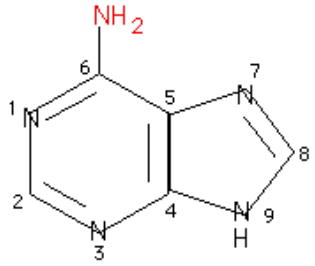


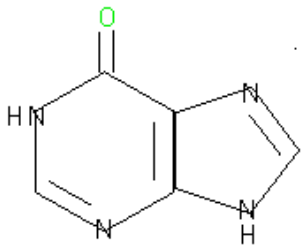


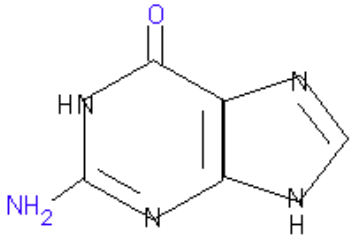


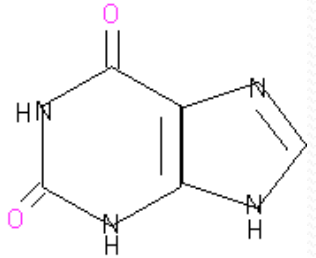


PURINAS

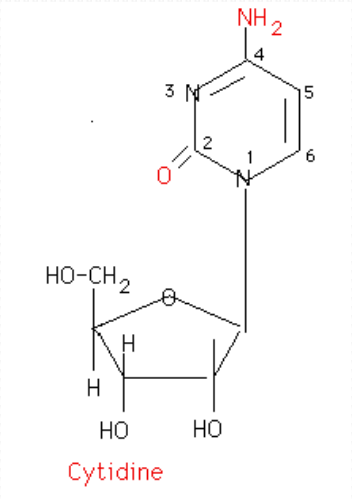




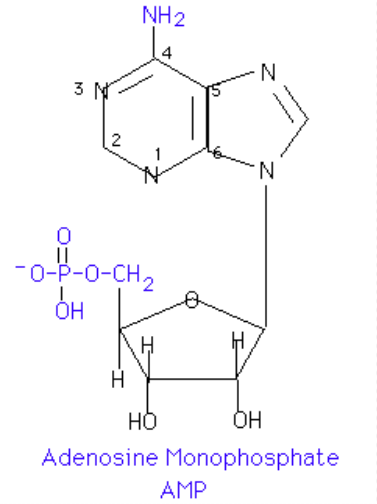




NUCLEOSIDO



NUCLEOTIDO



BIOQUÍMICA DEL ACIDO ÚRICO

7,9-dihidro-1H-purina-2,6,8(3H)-triona

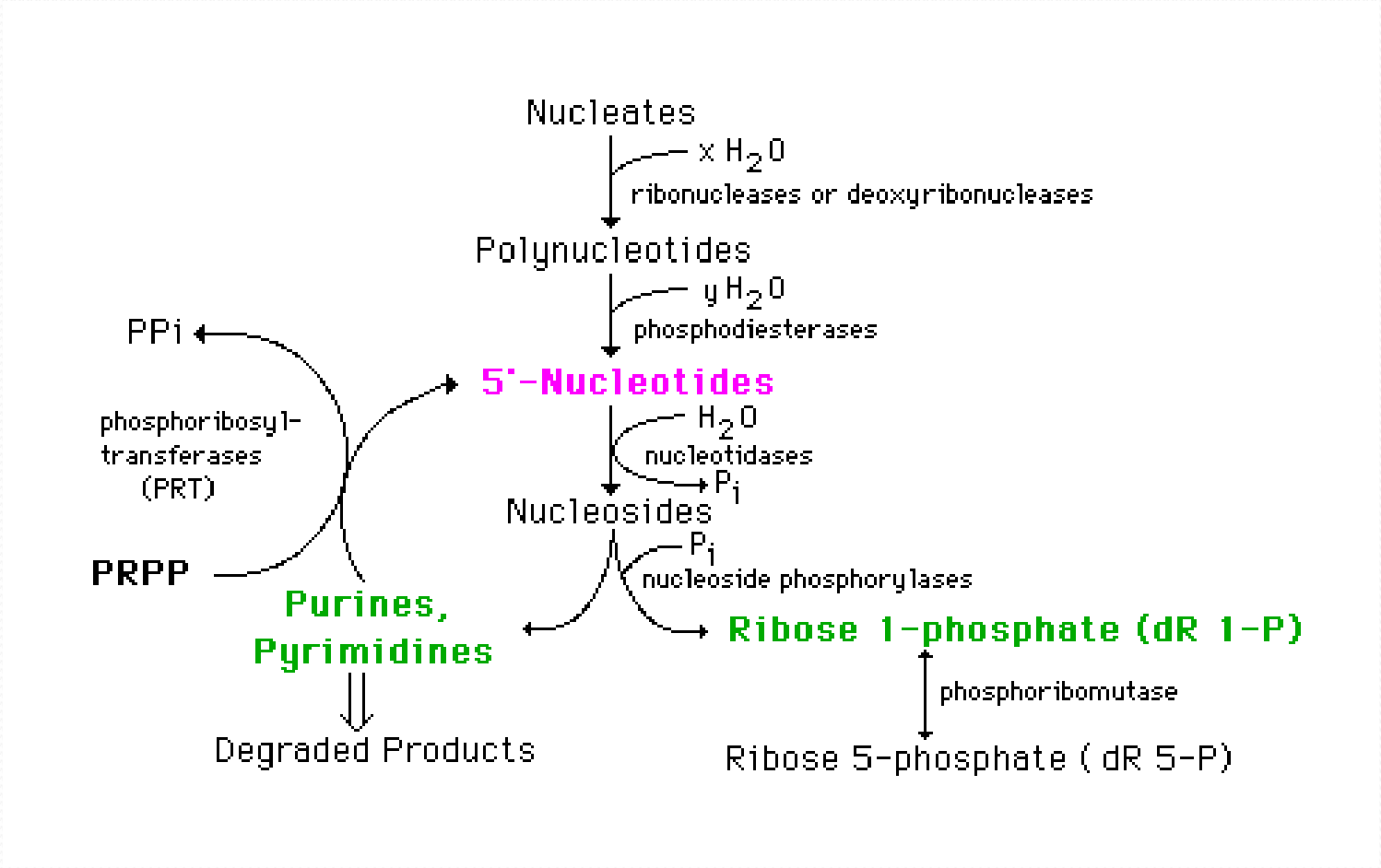
2,6,8 Trioxypurina

$C_5H_4N_4O_3$

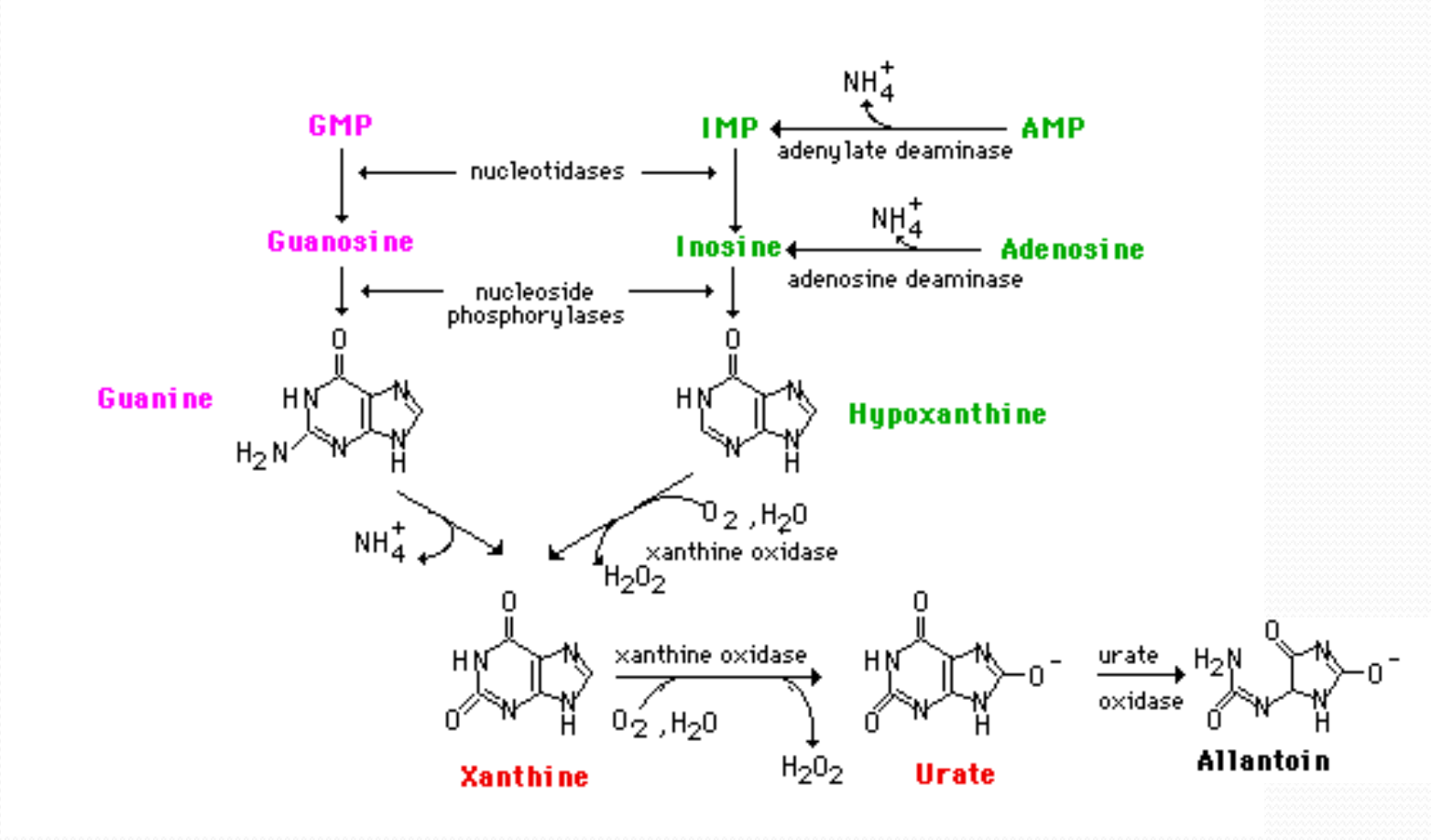
Producto final del metabolismo de las purinas en los humanos.

En la mayoría de vertebrados y mamíferos el metabolismo continúa hasta alantoína mediante la enzima URICASA

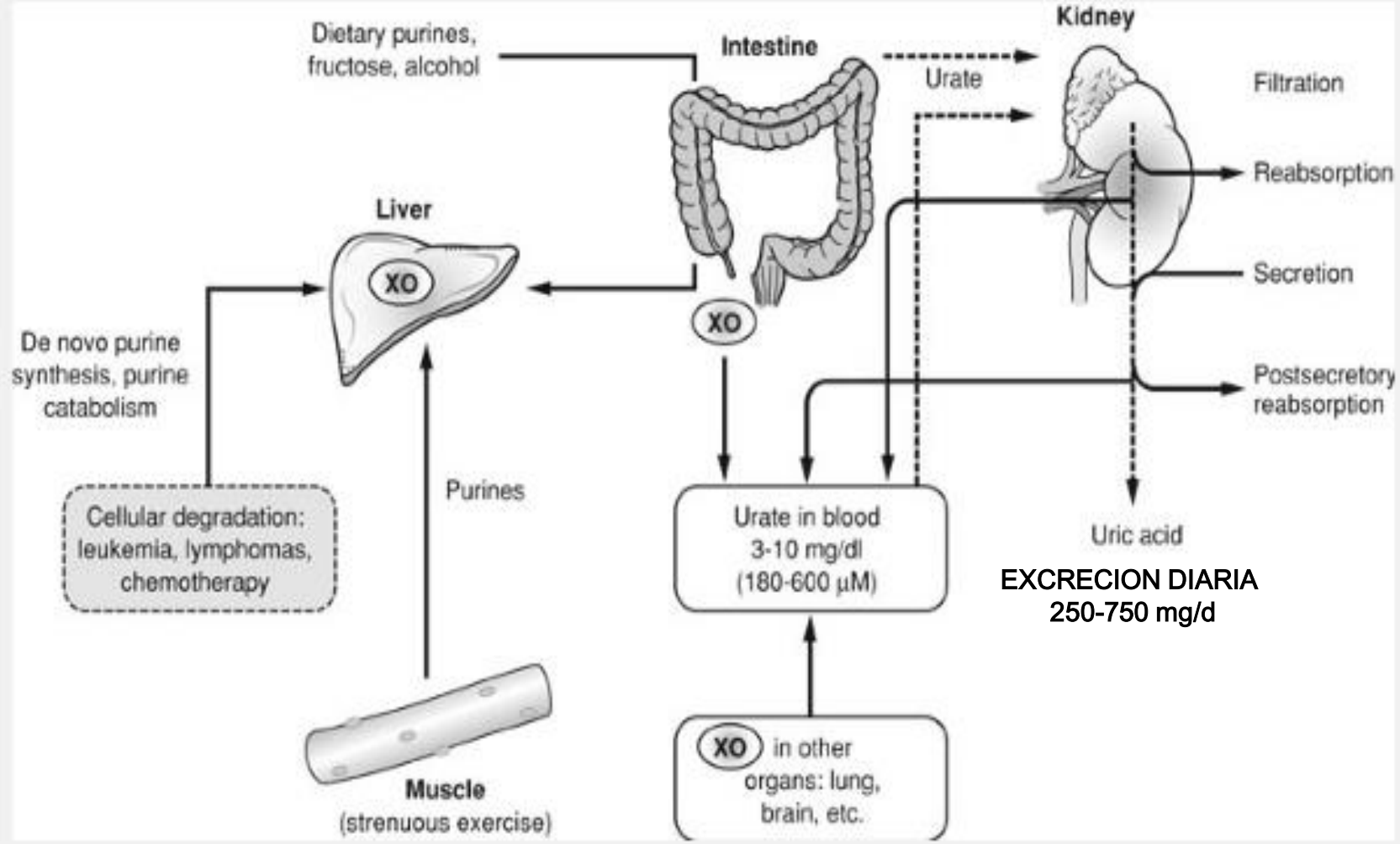
METABOLISMO DE NUCLEÓTIDOS



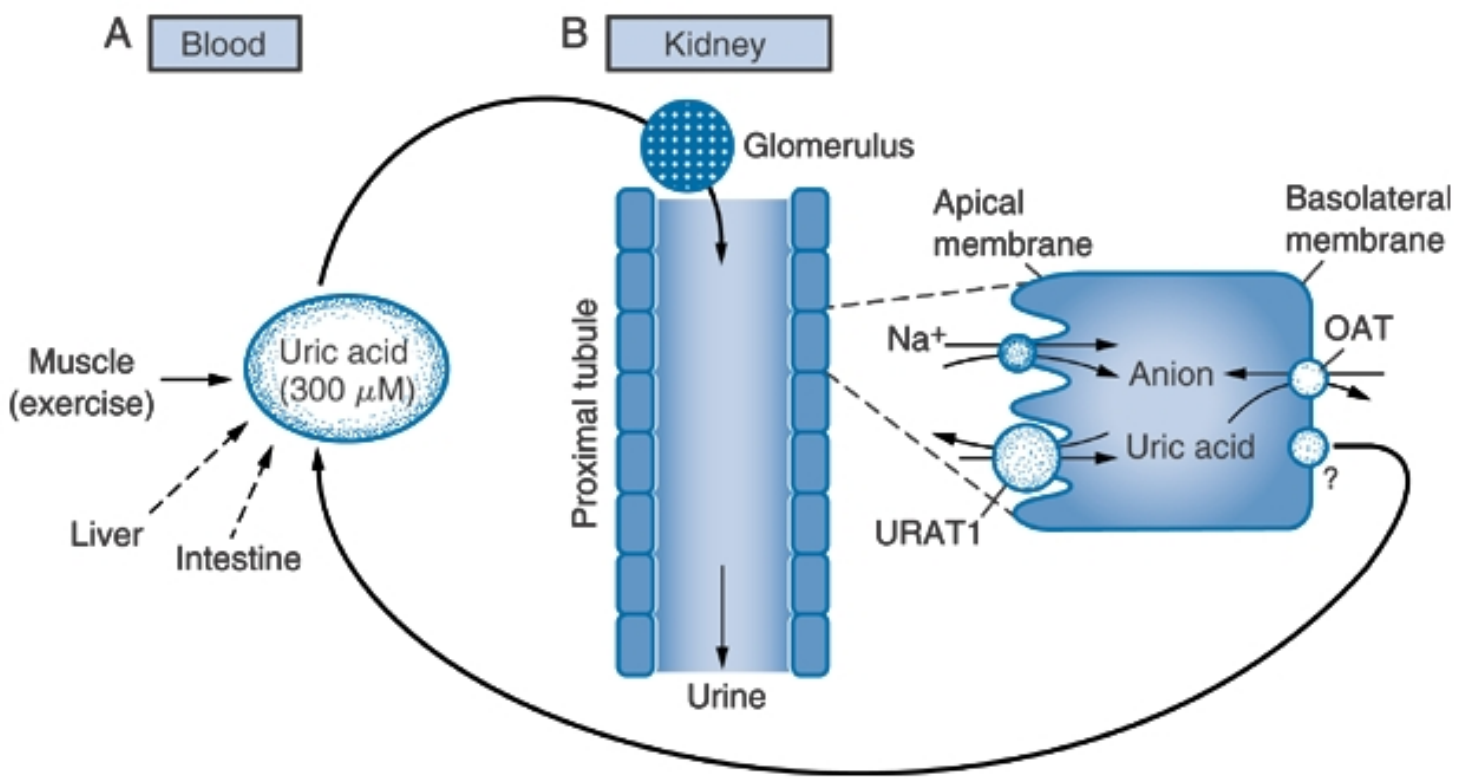
METABOLISMO DE LOS NUCLEÓTIDOS EN LOS VERTEBRADOS INFERIORES



METABOLISMO DEL ACIDO URICO

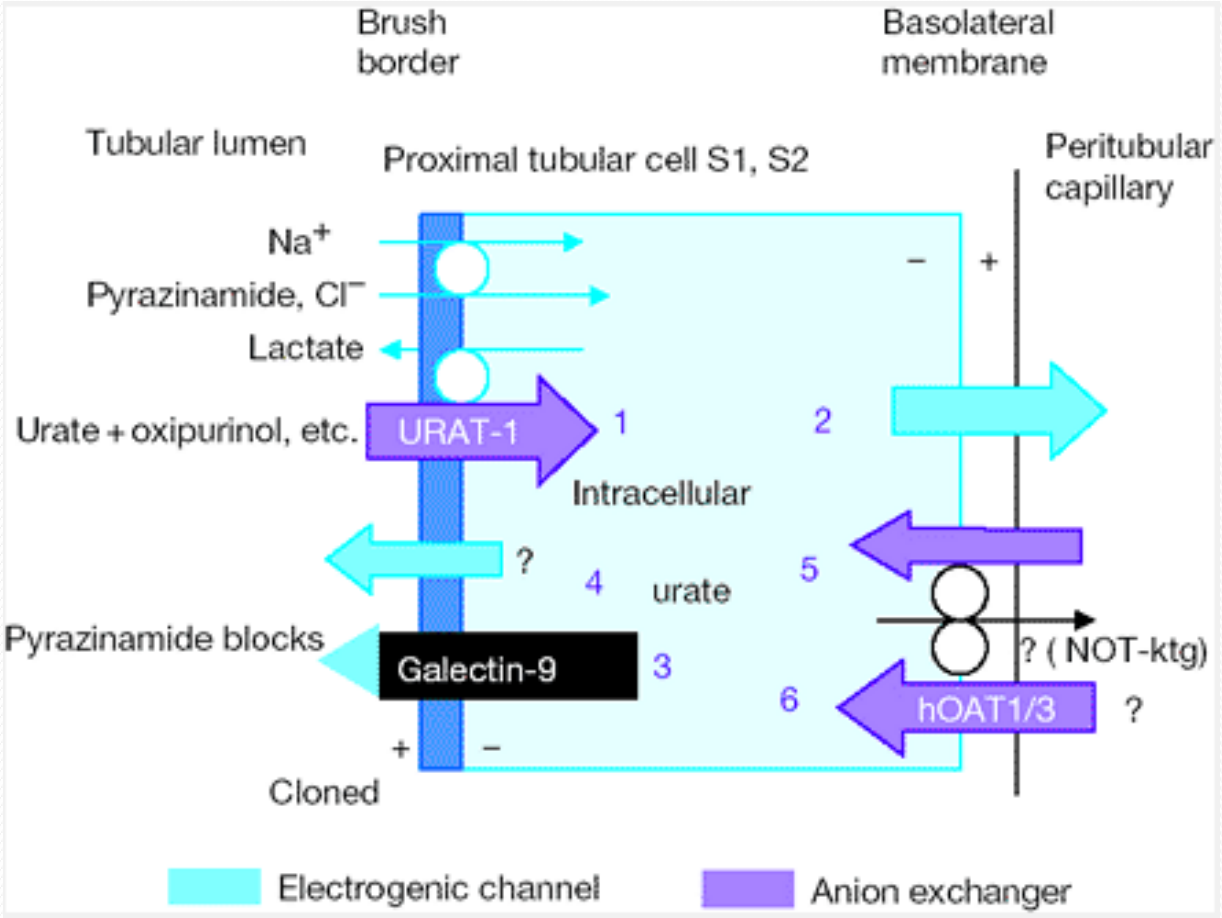


METABOLISMO DEL ACIDO URICO



(Modified from Hediger MA. Kidney function: Gateway to a long life? Nature 417:393, 2002.)

MECANISMOS DE TRANSPORTE RENAL



Uric Acid, Evolution and Primitive Cultures

Richard J. Johnson,* Srinivas Titte,* J. Robert Cade,* Bruce A. Rideout,† and William J. Oliver‡

- Pérdida de URICASA por los ancestros homínidos hace 8-20 millones de años, ¿Por qué?
  - Puede incrementar la inteligencia porque tiene similitudes estructurales con otros estimulantes cerebrales (cafeína)
  - Provee una potente actividad antioxidante (mayor longevidad)
  - **Para aumentar la presión arterial e incrementar la sensibilidad a la sal**

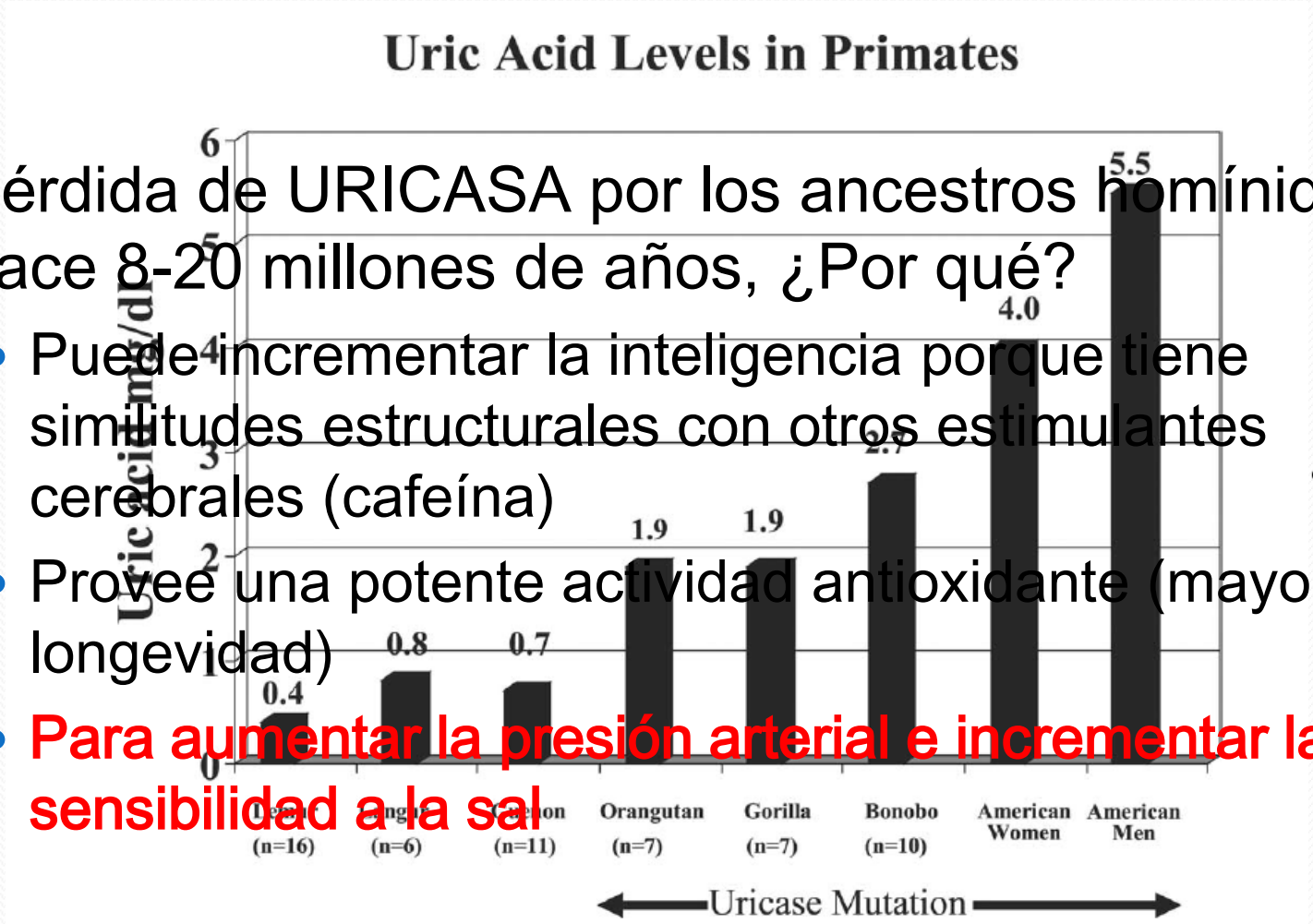
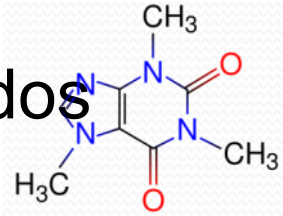
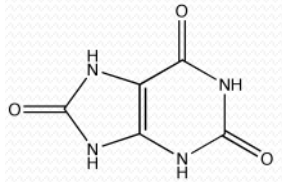


Figure 1 Mean serum uric acid levels of various primates obtained from the San Diego zoo. The values for mean uric acid in American men and women was obtained from the NHANES study.[77]



CAFEINA



AC. URICO

Semin Nephrol 25:3-8 © 2005

FISIOPATOLOGIA

HISTORIA

- Asociación entre Hipertensión e Hiperuricemia descrita desde 1879 por Frederick Akbar Mahomed.
  - *On chronic Bright´s disease, and its essential symptoms. Lancet I:399-401, 1879.*
- Huchard reportó que las principales causas de arterioloesclerosis eran gota e hiperuricemia
  - *Arterioloesclerosis: Including its cardiac form. JAMA 53:1129, 1909.*

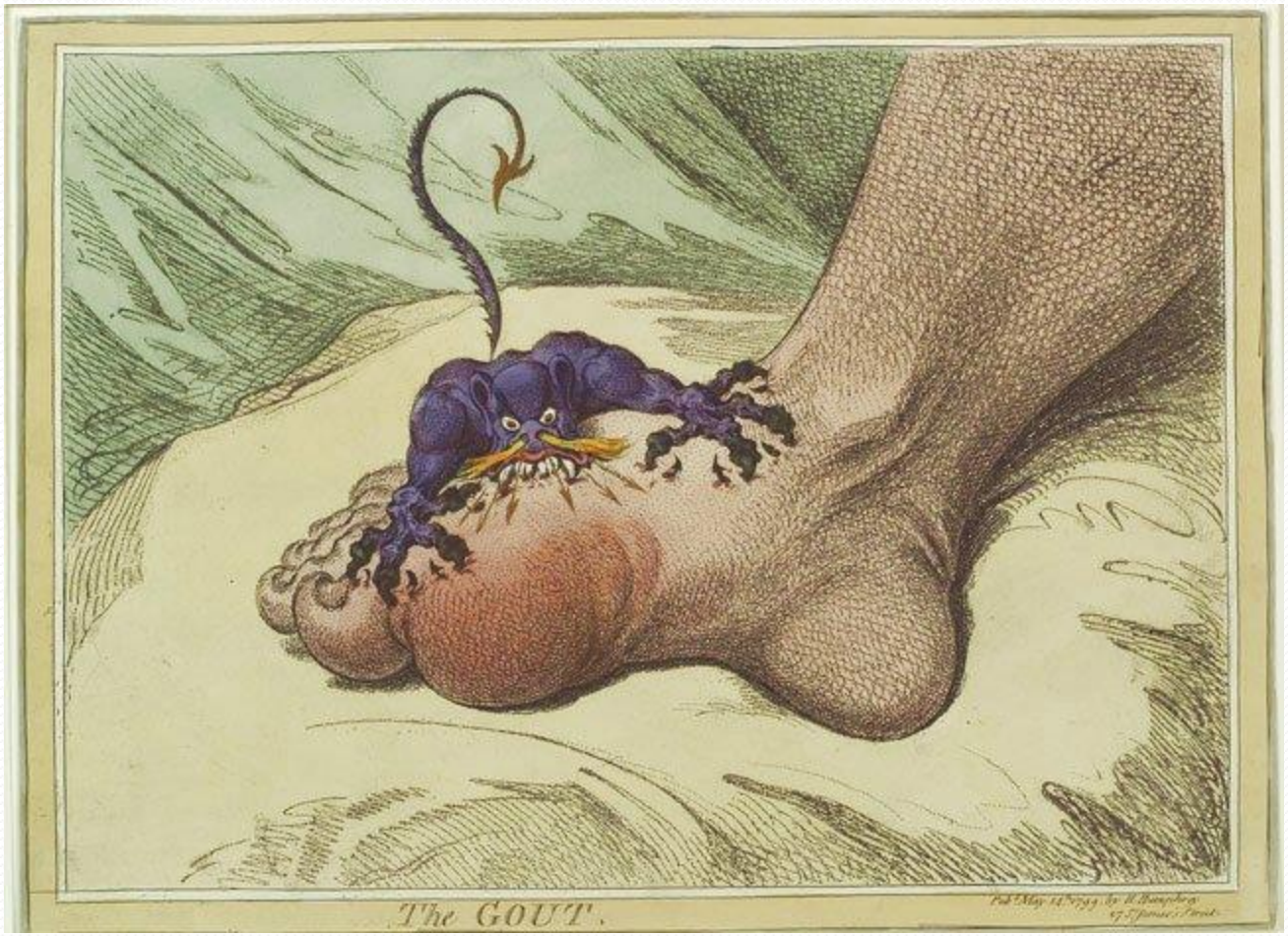
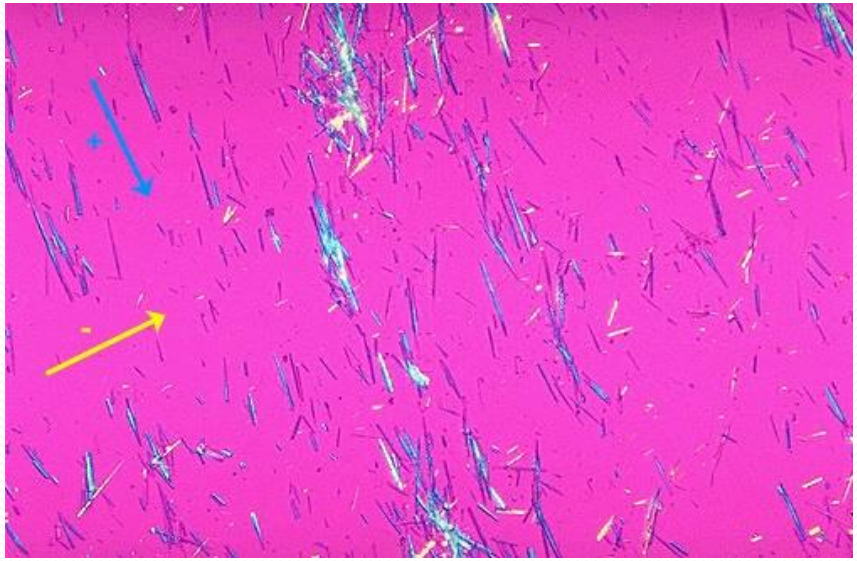
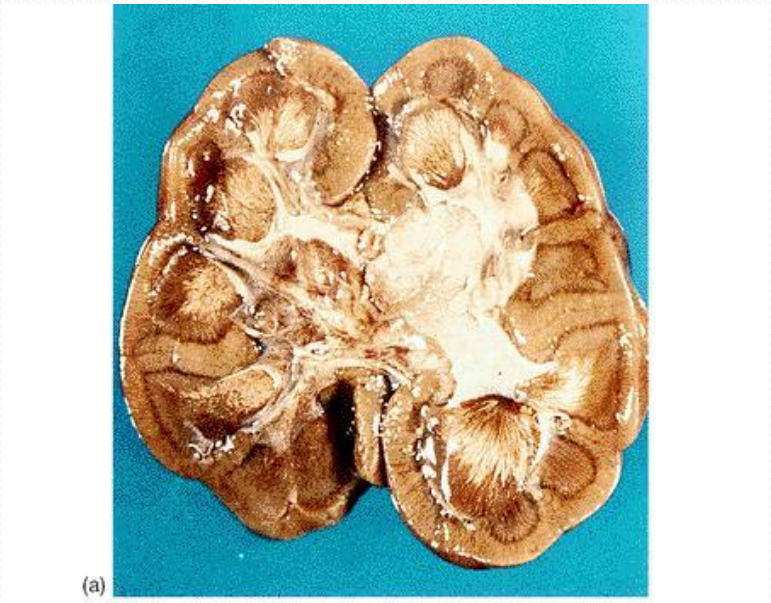
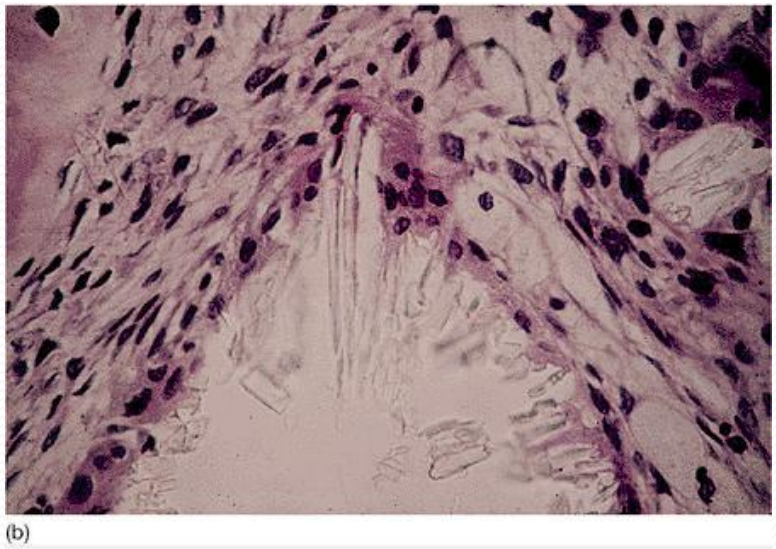

The GOUT.

TABLE 76-1 Major causes of hyperuricemia

- Genetic causes
  - Familial hyperuricemic nephropathy (mutation of uromodulin)
  - Lesch-Nyan syndrome (HGPRT mutation)
  - Phosphoribosyl pyrophosphate synthetase (PRPPS) mutation
- Dietary causes
  - Diet high in purines (organ meats, shellfish, fatty meats)
  - Diet high in fructose (high fructose corn syrup, table sugar, honey)
  - Ethanol
  - Low salt diet
- Drugs
  - Thiazides
  - Loop diuretics
  - Calcineurin inhibitors (cyclosporine > tacrolimus)
  - Pyrizinamide
  - Low-dose aspirin
- Volume depletion
- Hypoxia (systemic or tissue)
- Increased cell turnover (myeloproliferative disorders, polycythemia vera)
- Conditions associated with higher uric acid levels
  - Renal failure
  - Obesity/metabolic syndrome
  - Untreated hypertension
  - African American race
  - Preeclampsia
  - Vigorous exercise







- Caracteristicas histopatológicas de la “Nefropatia Gotosa”
  - Depósito de cristales de ácido úrico en intersticio de manera dispersa
  - Arterioloesclerosis

- El ácido úrico se considera solo un marcador de enfermedad renal y cardiovascular y no como un factor de riesgo independiente para estas enfermedades.

- Evidencia epidemiológica, experimental, clínica.

Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism

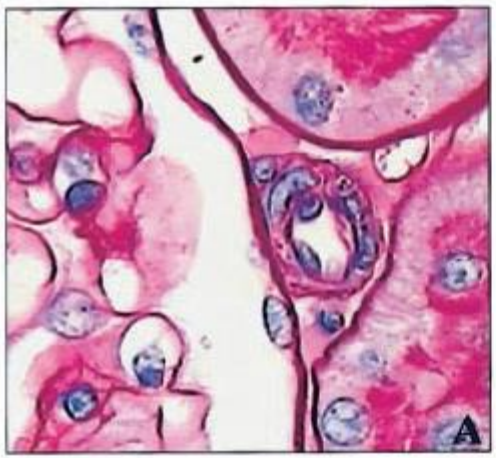
MARILDA MAZZALI, JOHN KANELLIS, LIN HAN, LILI FENG, YI-YANG XIA, QIANG CHEN, DUK-HEE KANG, KATHERINE L. GORDON, SUSUMU WATANABE, TAKAHIKO NAKAGAWA, HUI Y. LAN, AND RICHARD J. JOHNSON

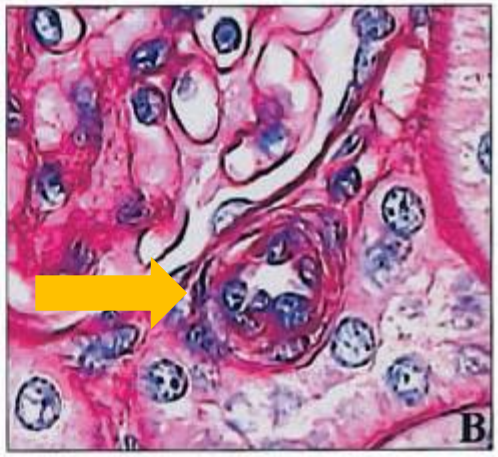
Division of Nephrology, Baylor College of Medicine, Houston, Texas 77030

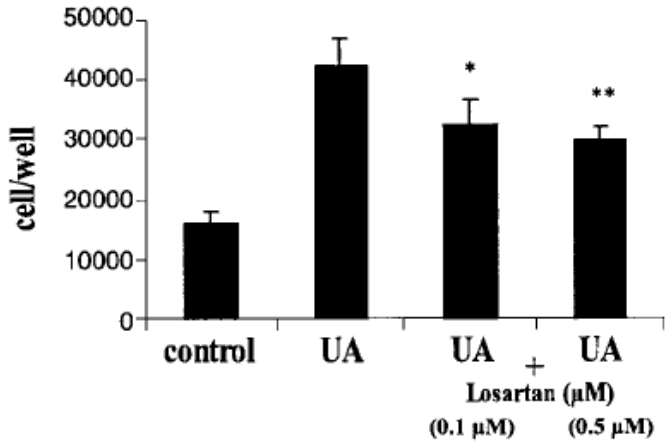
Table 1. *Hyperuricemia is associated with afferent arteriolopathy*

	Control*	Oxonic Acid (2%)	Allopurinol, 150 mg/l	Benziodarone, 15 mg/kg
Serum uric acid, mg/dl	1.39 ± 0.07	1.84 ± 0.21†	1.32 ± 0.06	1.40 ± 0.13
Systolic blood pressure, mmHg	126.8 ± 4.9	146.9 ± 8.5†	119.3 ± 5.6	127.8 ± 6.3
Arteriolar area, μm^2	128.1 ± 13.4	170.7 ± 20.1†	127.8 ± 4.9	139.1 ± 8.6
Media-to-lumen ratio	3.07 ± 0.24	4.28 ± 0.29†	3.10 ± 0.37	3.15 ± 0.17
Blood urea nitrogen, mg/dl	15.6 ± 3.8	20.5 ± 3.8†	11.8 ± 1.8	12.2 ± 3.5

*Low-salt diet. †$P < 0.05$ vs. other groups.





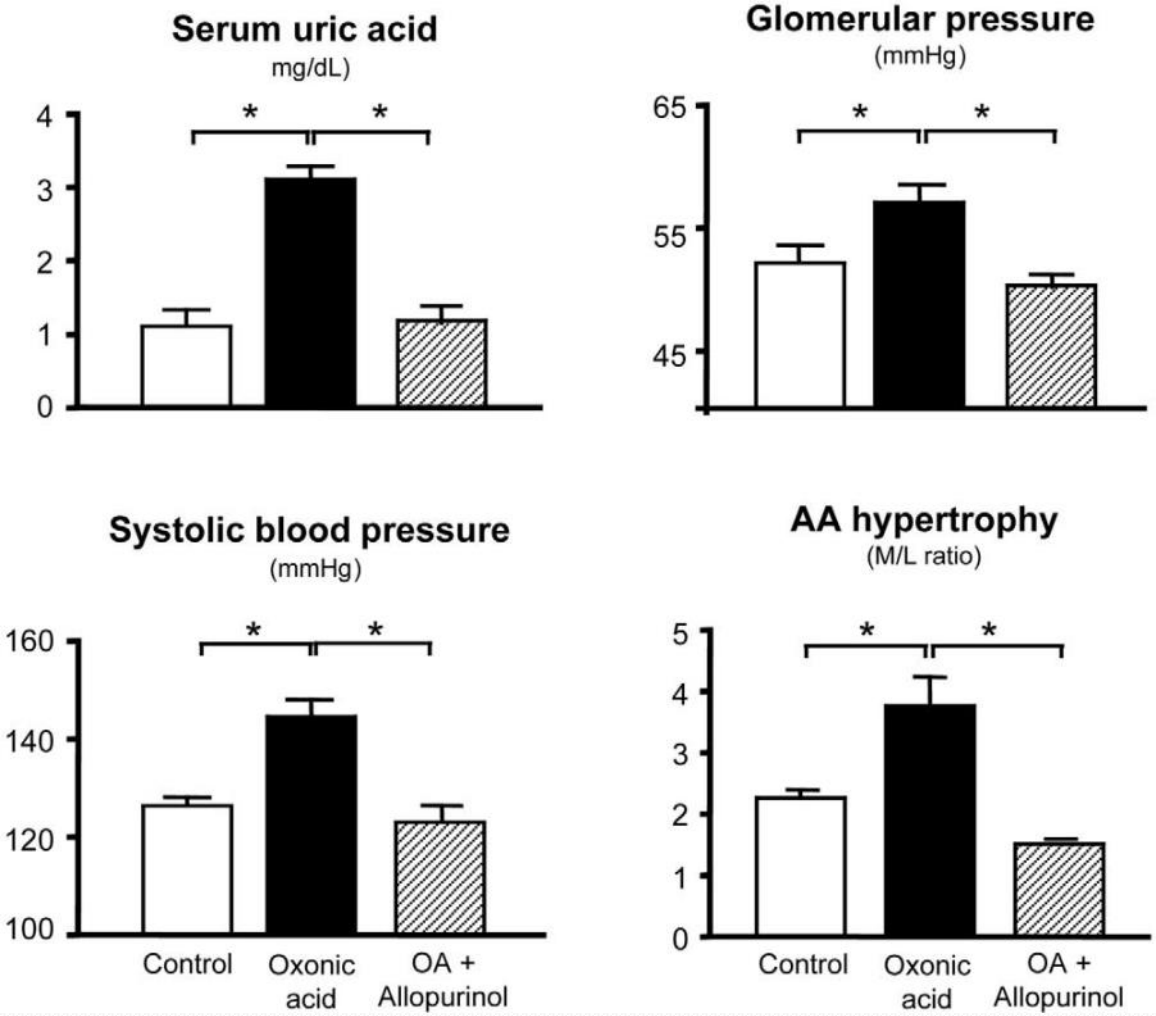


*P>0.05, **P<0.01 UA vs UA+Losartan(0.1, 0.5μM)

Am J Physiol Renal Physiol 282: F991–F997, 2002.

Hemodynamics of Hyperuricemia

Laura G. Sánchez-Lozada,* Edilia Tapia,* Bernardo Rodríguez-Iturbe,* Richard J. Johnson,† and Jaime Herrera-Acosta‡



Semin Nephrol 25:19-24 © 2005

Uric Acid – A Uremic Toxin?

Takahiko Nakagawa Marilda Mazzali Duk-Hee Kang
L. Gabriela Sánchez-Lozada Jaime Herrera-Acosta Richard J. Johnson

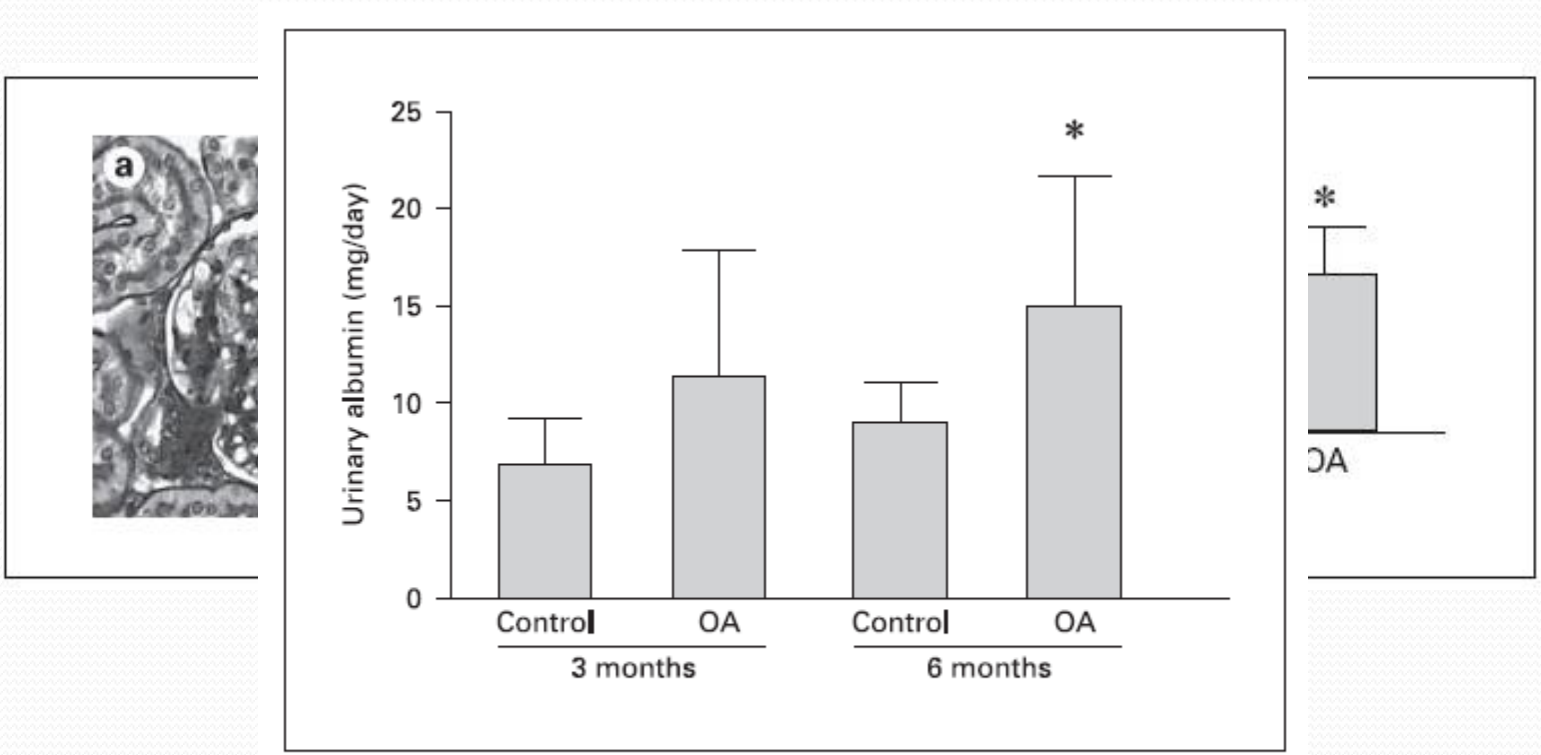


Fig. 2. Prolonged hyperuricemia is associated with the development of microalbuminuria. * $p < 0.05$ versus control (6 months).

Blood Purif 2006;24:67–70

Uric Acid and Endothelial Dysfunction in Essential Hypertension

Carmine Zoccali,* Raffaele Maio,† Francesca Mallamaci,* Giorgio Sesti,† and Francesco Perticone†

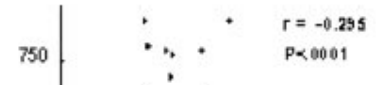
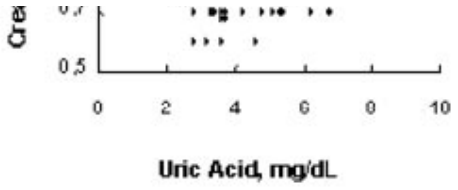
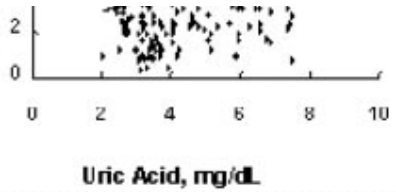


Table 3. Multivariate logistic analysis of endothelial dysfunction[a]

	HR	95% CI	*P*
Creatinine (mg/dl)	1.475	1.137 to 1.911	0.003
HOMA	1.422	1.101 to 1.836	0.006
UA (mg/dl)	1.412	1.110 to 1.796	0.004
Systolic BP (mmHg)	1.035	1.000 to 1.071	0.045
CRP (mg/L)	1.180	0.989 to 1.407	0.064
Male gender	1.440	0.687 to 3.021	0.333
Pulse pressure (mmHg)	1.026	0.981 to 1.073	0.257
Age (yr)	1.019	0.985 to 1.054	0.271
Diastolic BP (mmHg)	0.974	0.931 to 1.019	0.257
Triglycerides (mg/dl)	1.002	0.993 to 1.011	0.612
Body mass index (kg/m^2)	1.018	0.921 to 1.126	0.719
HDL Cholesterol (mg/dl)	0.998	0.968 to 1.028	0.900
LDL cholesterol (mg/dl)	0.994	0.983 to 1.005	0.310
Smokers	1.011	0.446 to 2.291	0.978

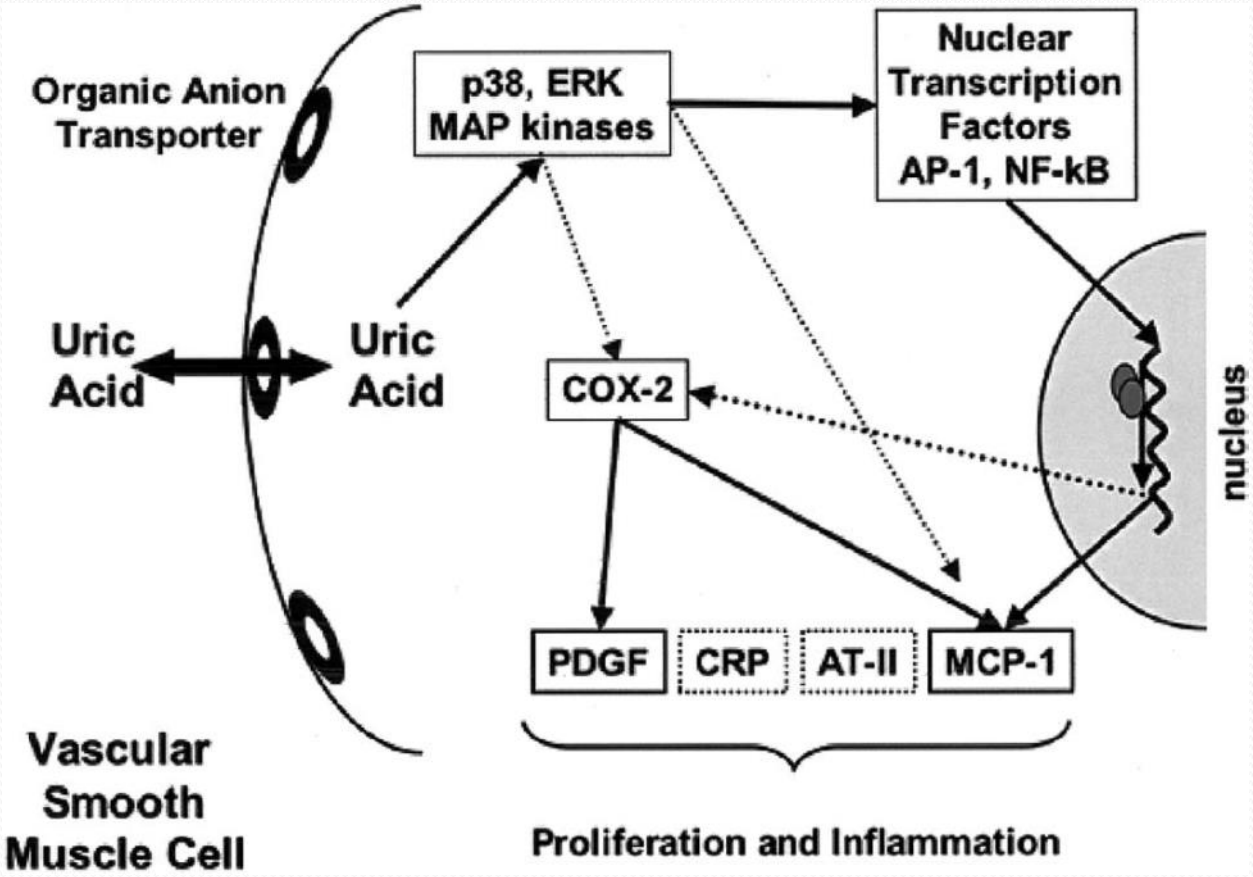




J Am Soc Nephrol 17: 1466–1471, 2006.

Uric Acid as a Mediator of Endothelial Dysfunction, Inflammation, and Vascular Disease

John Kanellis and Duk-Hee Kang



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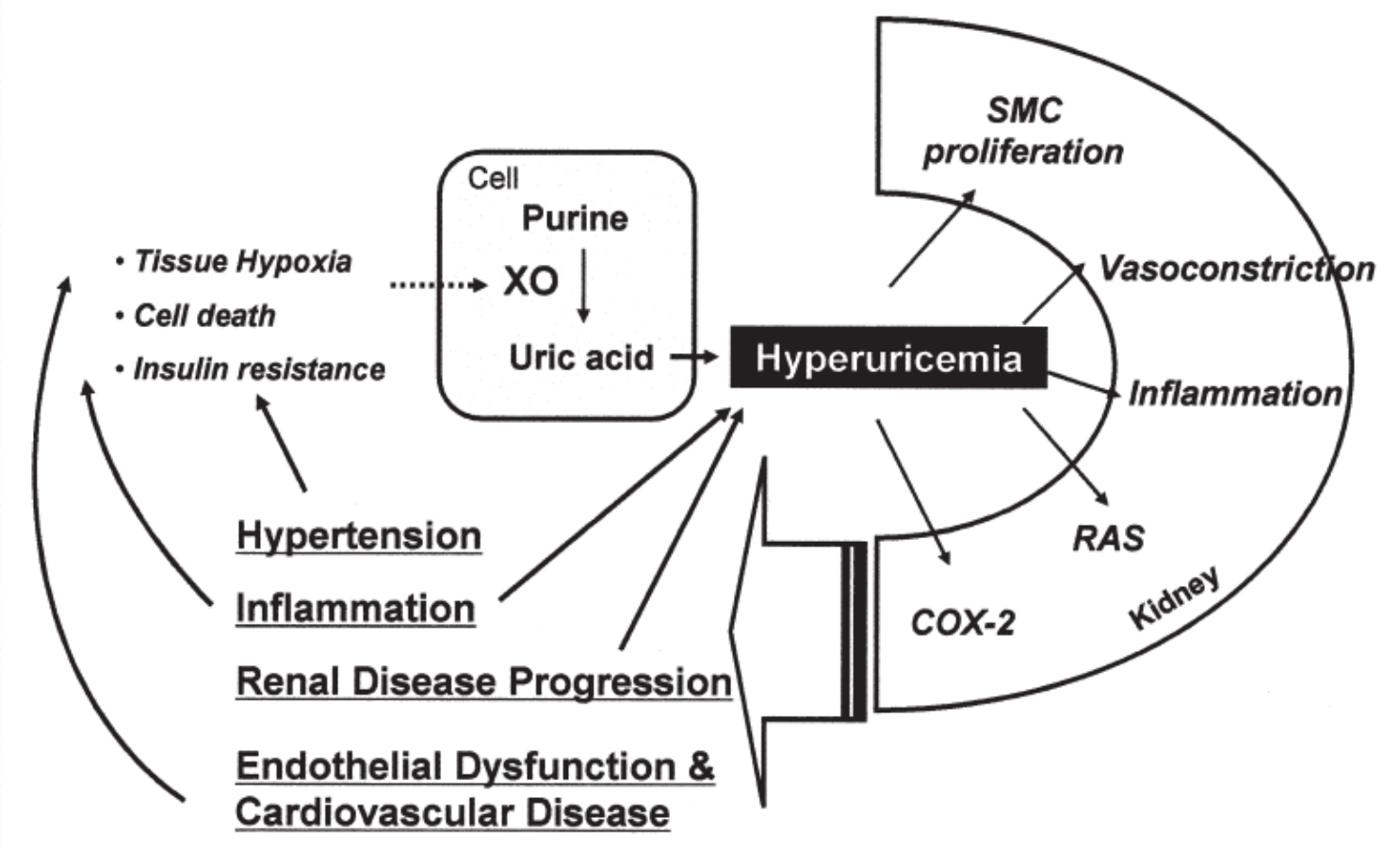
Uric Acid and Chronic Renal Disease: Possible Implication of Hyperuricemia on Progression of Renal Disease

Duk-Hee Kang and Takahiko Nakagawa



Semin Nephrol 25:43-49 © 2005

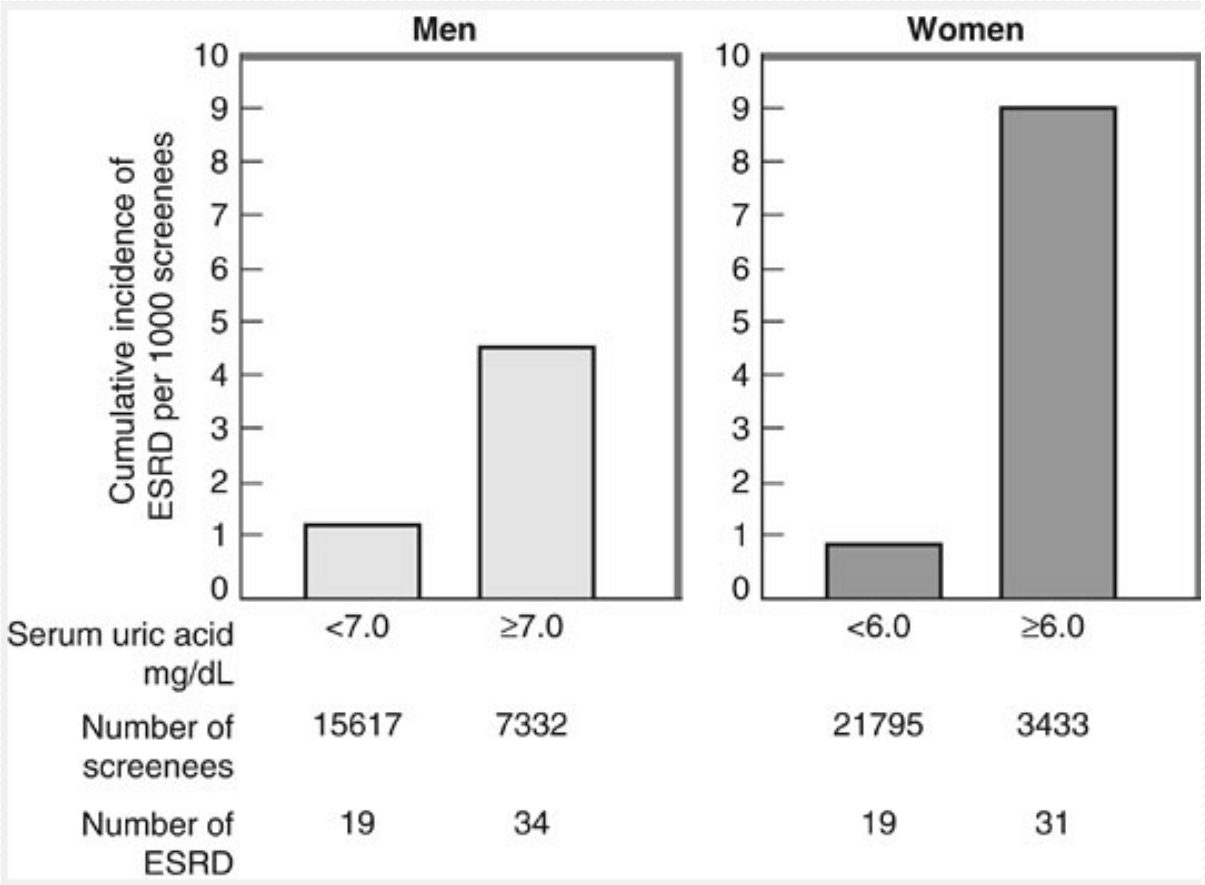
Serum Uric Acid: A Risk Factor and a Target for Treatment?

Daniel I. Feig,* Marilda Mazzali,† Duk-Hee Kang,‡ Takahiko Nakagawa,§ Karen Price,§ John Kannelis,‖ and Richard J. Johnson§

Table 1. Epidemiological studies that suggested that serum uric acid predicts hypertension

Author	Year Published	Study Size	Duration of Follow-Up (yr)	Increased Risk
Kahn *et al.* (25)	1972	10,000 men	5	2-fold
Selby *et al.* (29)	1990	2062 adults	6	3-fold
Hunt *et al.* (28)	1991	1482 adults	7	2-fold
Jossa *et al.* (27)	1994	619 men	12	1.2-fold
Taniguchi *et al.* (30)	2001	6356 men	10	2-fold
Masuo *et al.* (31)	2003	433 men	5	+27 mmHg in systolic BP per each 1-mg/dl change in uric acid
Nakanishi *et al.* (32)	2003	2310 men	6	1.6-fold
Nagahama *et al.* (40)	2004	4489 adults	23	1.5-fold in men 1.9-fold in women
Alper *et al.* (33)	2005	577 children	11	Predicts diastolic hypertension
Sundstrom *et al.* (34)	2005	3119 adults	4	1.5-fold

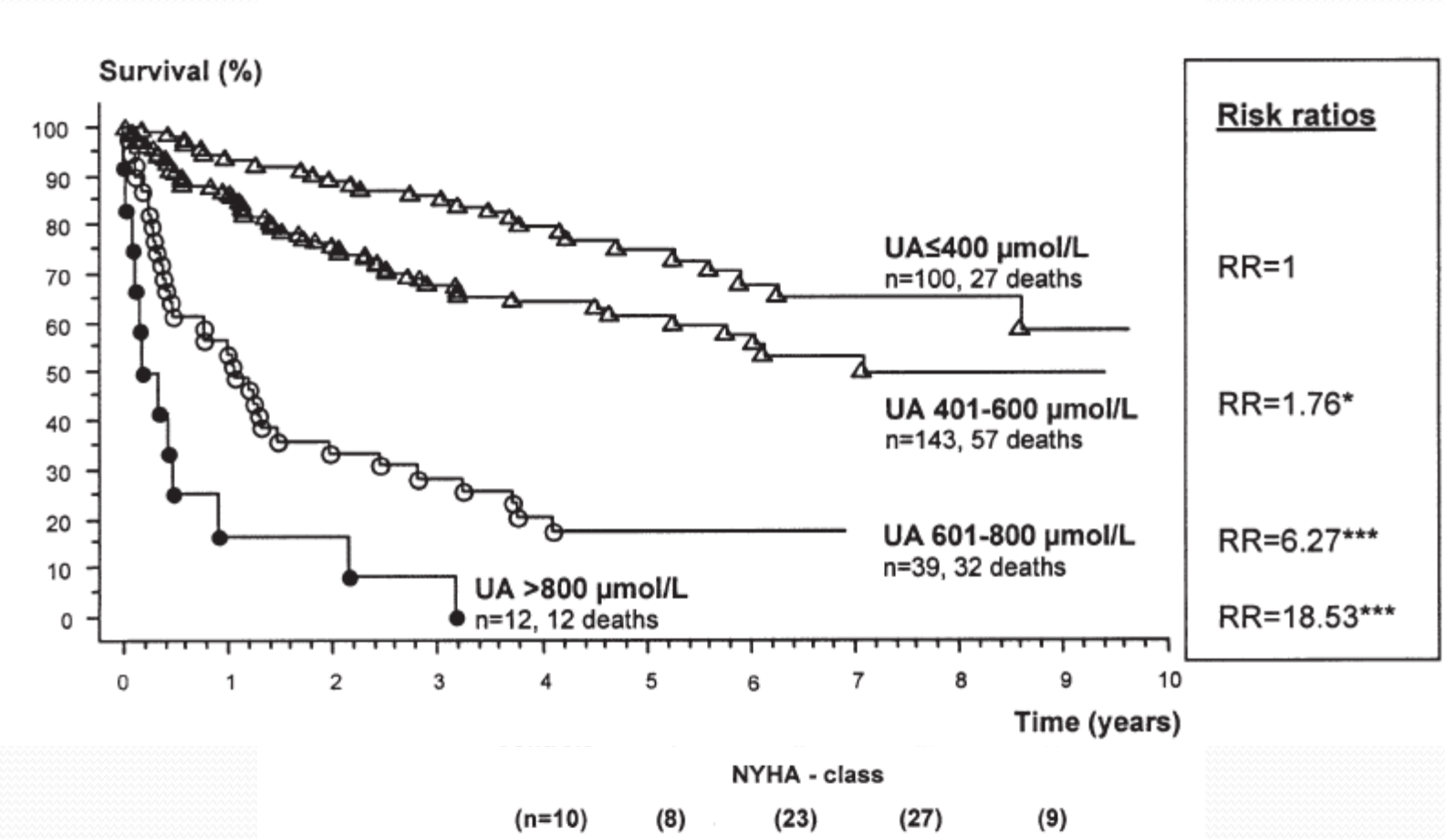
J Am Soc Nephrol 17: S69–S73, 2006



Am J Kidney Dis 2004;44:642

Uric Acid in Chronic Heart Failure

Wolfram Doehner* and Stefan D. Anker*,†

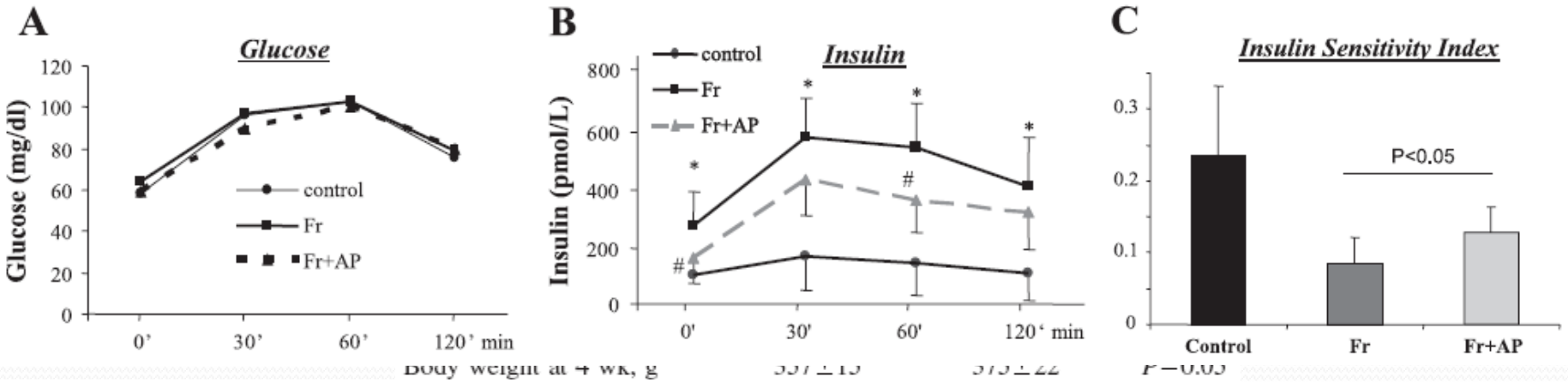


Semin Nephrol 24:61-66 © 2005

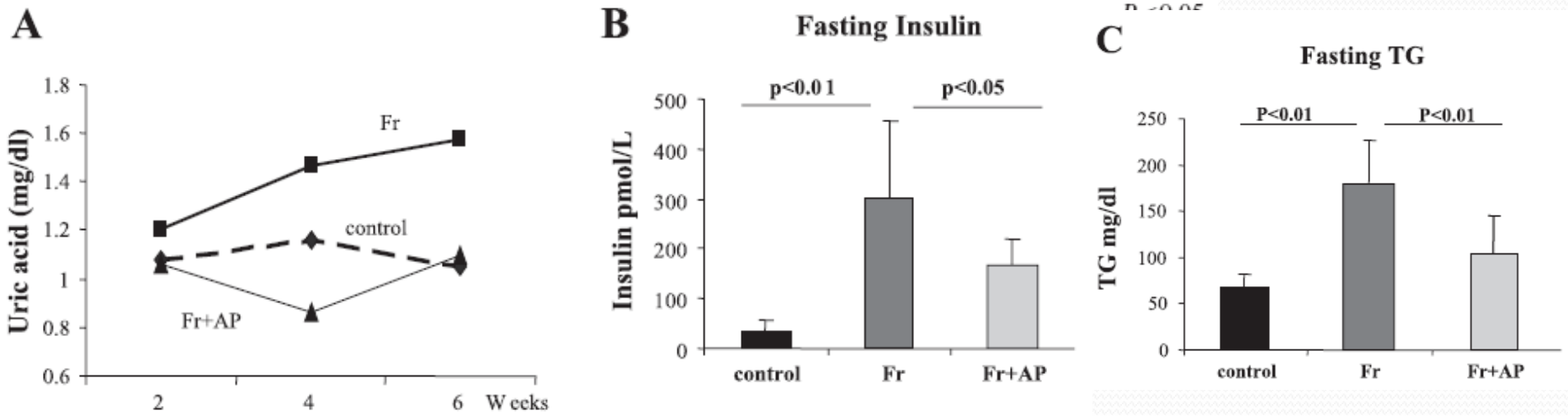
ACIDO URICO Y SINDROME METABOLICO

A causal role for uric acid in fructose-induced metabolic syndrome

Takahiko Nakagawa,[1] Hanbo Hu,[1] Sergey Zharikov,[1] Katherine R. Tuttle,[2]
Robert A. Short,[2,3] Olena Glushakova,[1] Xiaosen Ouyang,[1] Daniel I. Feig,[4]
Edward R. Block,[1] Jaime Herrera-Acosta,[5,†] Jawaharlal M. Patel,[1] and Richard J. Johnson[1]



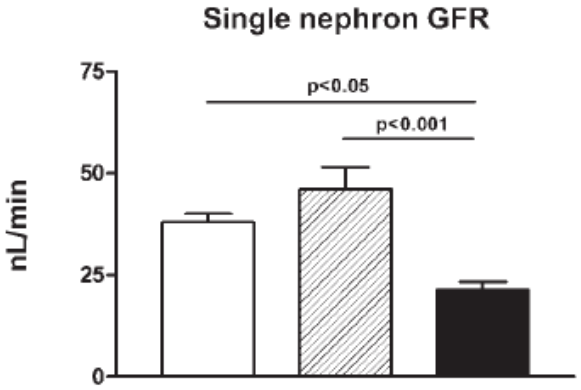
Body weight at 4 wk, g 337 ± 13 373 ± 22

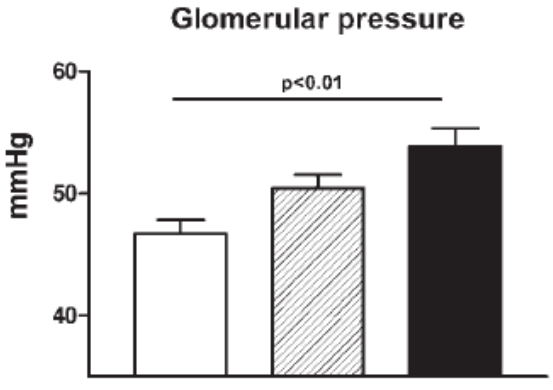


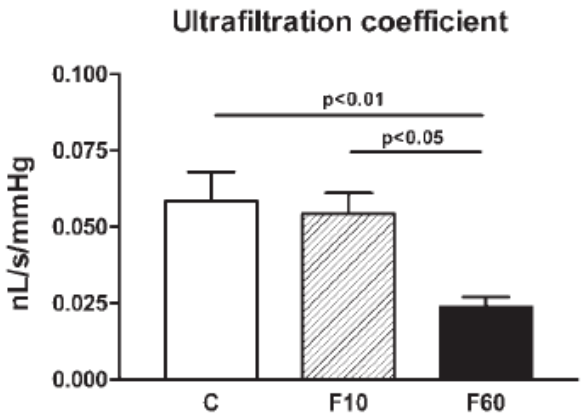
Am J Physiol Renal Physiol 290: F625–F631, 2006.

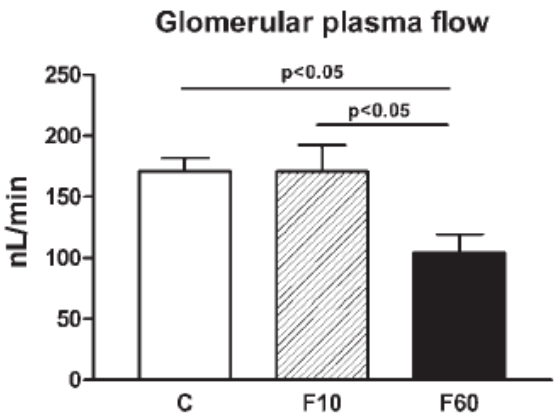
Fructose-induced metabolic syndrome is associated with glomerular hypertension and renal microvascular damage in rats

Laura G. Sánchez-Lozada,[1] Edilia Tapia,[1] Adriana Jiménez,[1] Pablo Bautista,[1] Magdalena Cristóbal,[1] Tomás Nepomuceno,[1] Virgilia Soto,[2] Carmen Ávila-Casado,[2] Takahiko Nakagawa,[3] Richard J. Johnson,[3] Jaime Herrera-Acosta,[1]† and Martha Franco[1]







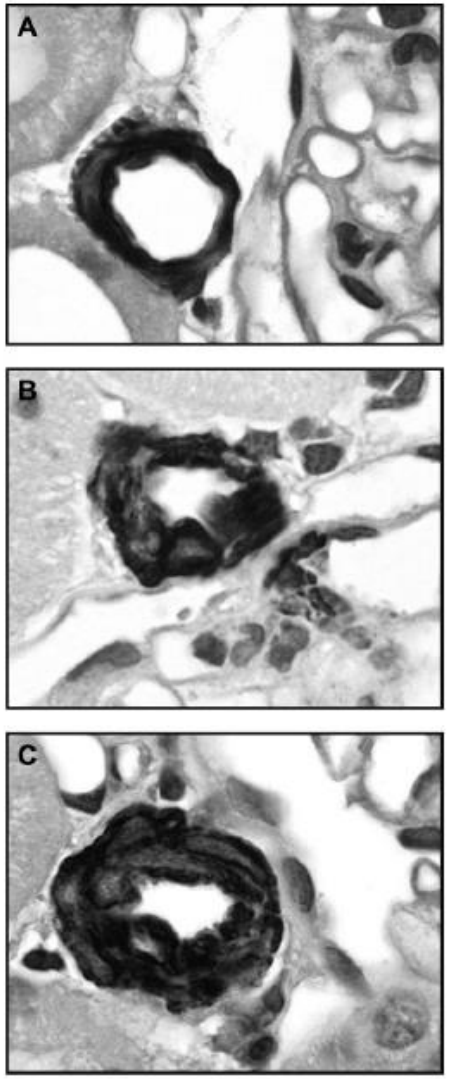


cose

g/dl

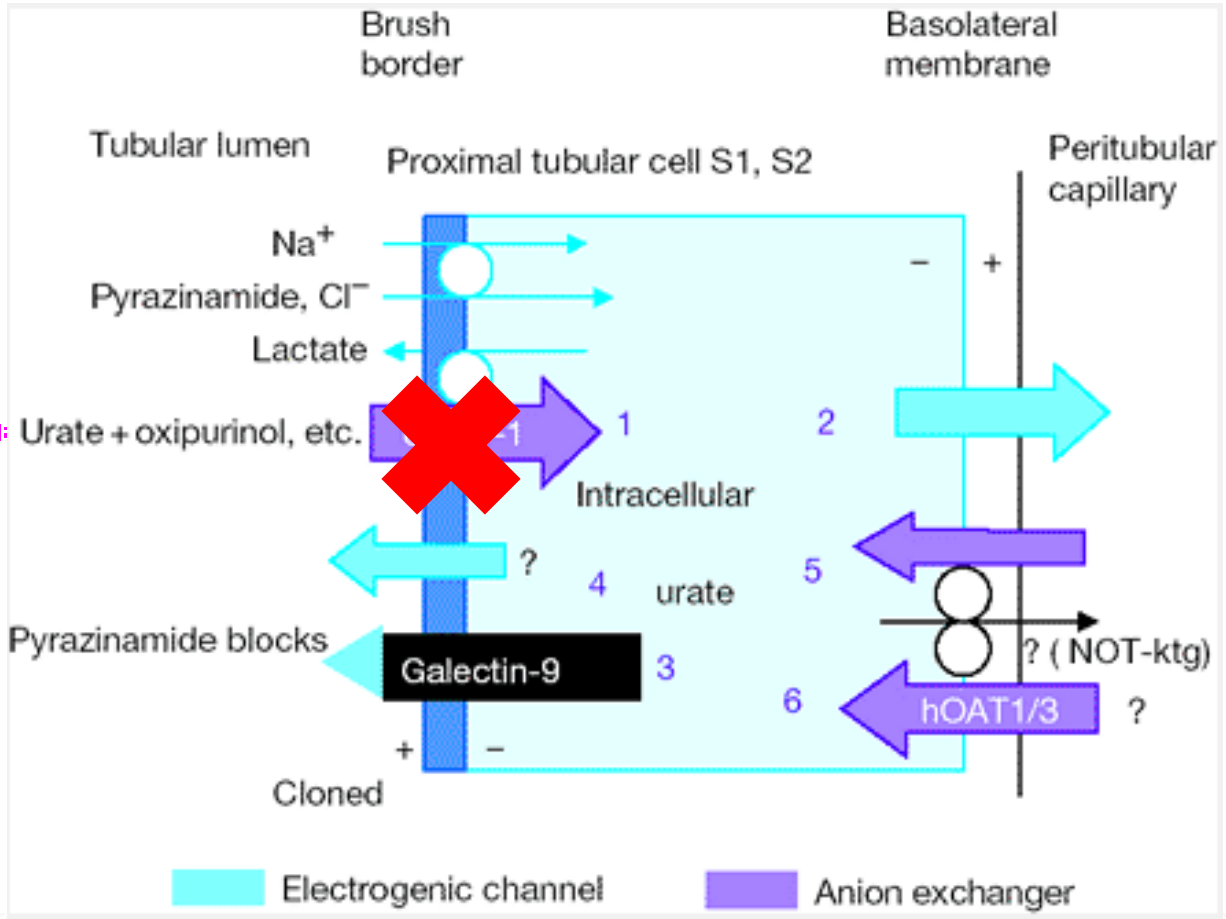
8.5
8.3
16.5†

blood
5 vs. F



Am J Physiol Renal Physiol 292: F423–F429, 2007.

TRATAMIENTO


Brush border
Basolateral membrane
Tubular lumen
Proximal tubular cell S1, S2
Peritubular capillary
Na+
Pyrazinamide, Cl−
Lactate
Urate + oxipurinol, etc.
1
2
Intracellular
?
4
urate
5
Pyrazinamide blocks
Galectin-9
3
? (NOT-ktg)
6
hOAT1/3
?
+
−
Cloned
Electrogenic channel
Anion exchanger

SUSTANCIAS QUE MODIFICAN LA EXCRECION DEL ACIDO URICO

ENDOGENAS

- *DISMINUYEN LA EXCRECION*
  - Lactato
  - Hidroxibutirato
  - Acetoacetato
- *AUMENTAN LA EXCRECION*
  - Embarazo

EXOGENAS

- Salicilatos
- Pirazinamida
- Nicotinato
- Etambutol
- Plomo
- Berilio
- Diuréticos
- Ciclosporina
- Infusión salina
- Sulfinpirazona
- Benzbromarona
- Fenilbutazona
- Probenecid
- Agentes radiocontraste
- Fenofibrato
- Losartan

Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

Yui-Pong Siu, MRCP, Kay-Tai Leung, MRCP, Matthew Ka-Hang Tong, MRCP, and Tze-Hoi Kwan, FRCP

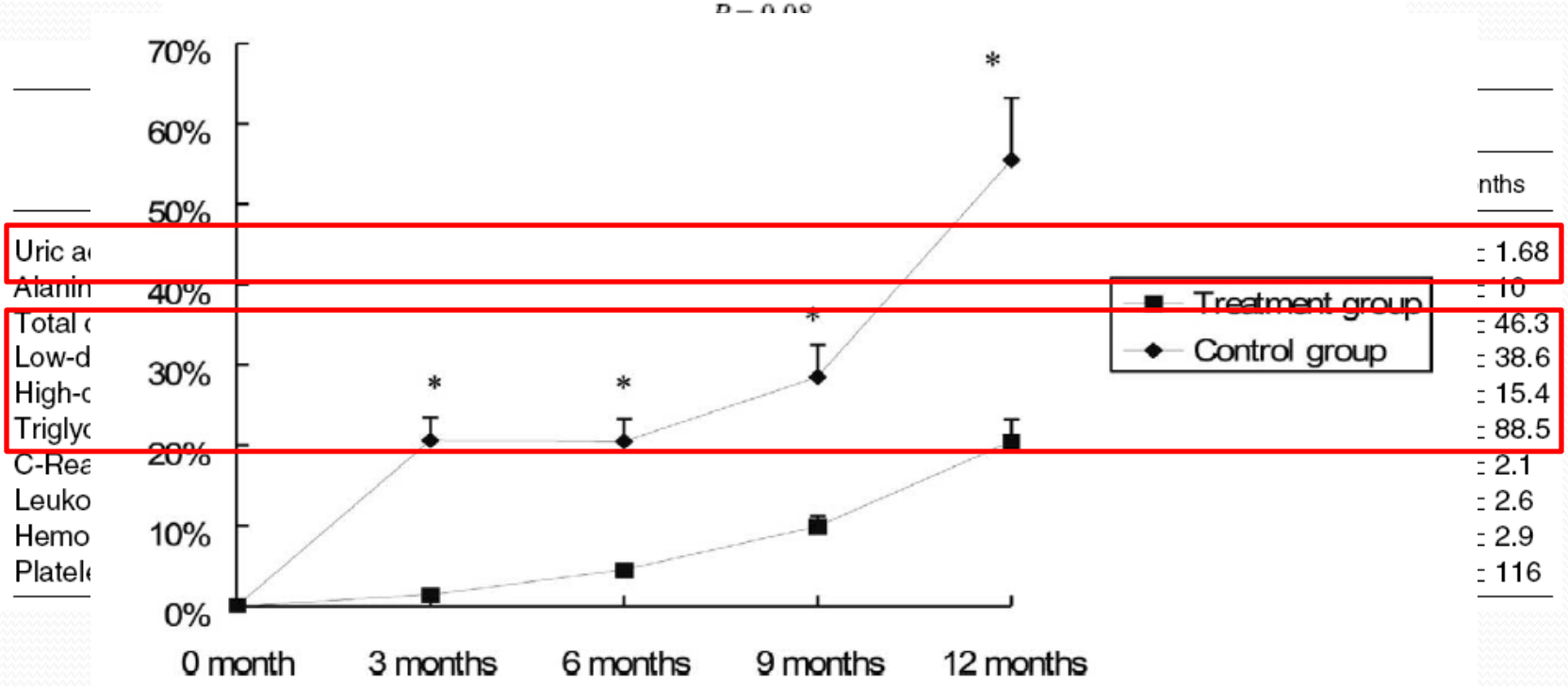
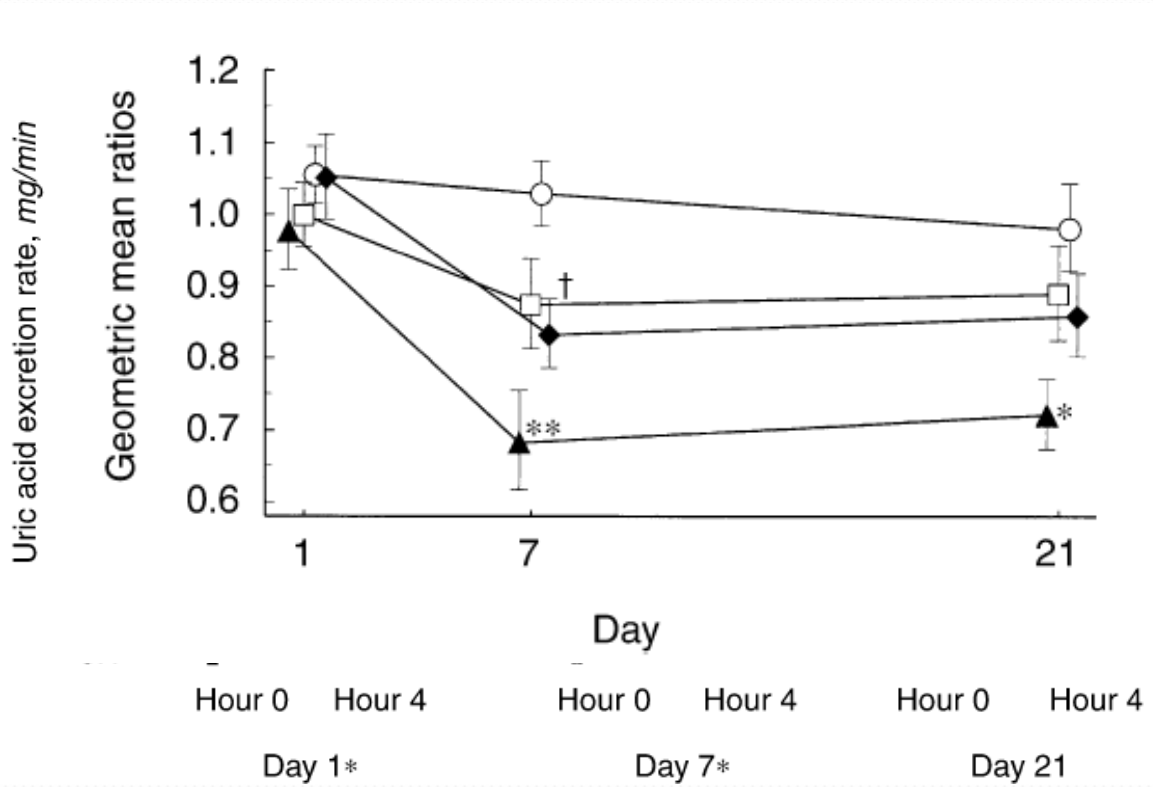


Fig 5. Mean percentage of change in Cr levels in the treatment and control groups. *$P < 0.05$ compared with baseline.

Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia

SHAHNAZ SHAHINFAR, ROGER L. SIMPSON, ALEXANDRA D. CARIDES, BALASAMY THIYAGARAJAN, YASUSHI NAKAGAWA, JASON G. UMANS, JOAN H. PARKS, and FREDRIC L. COE, for the LOSARTAN URIC ACID STUDY GROUP[1]

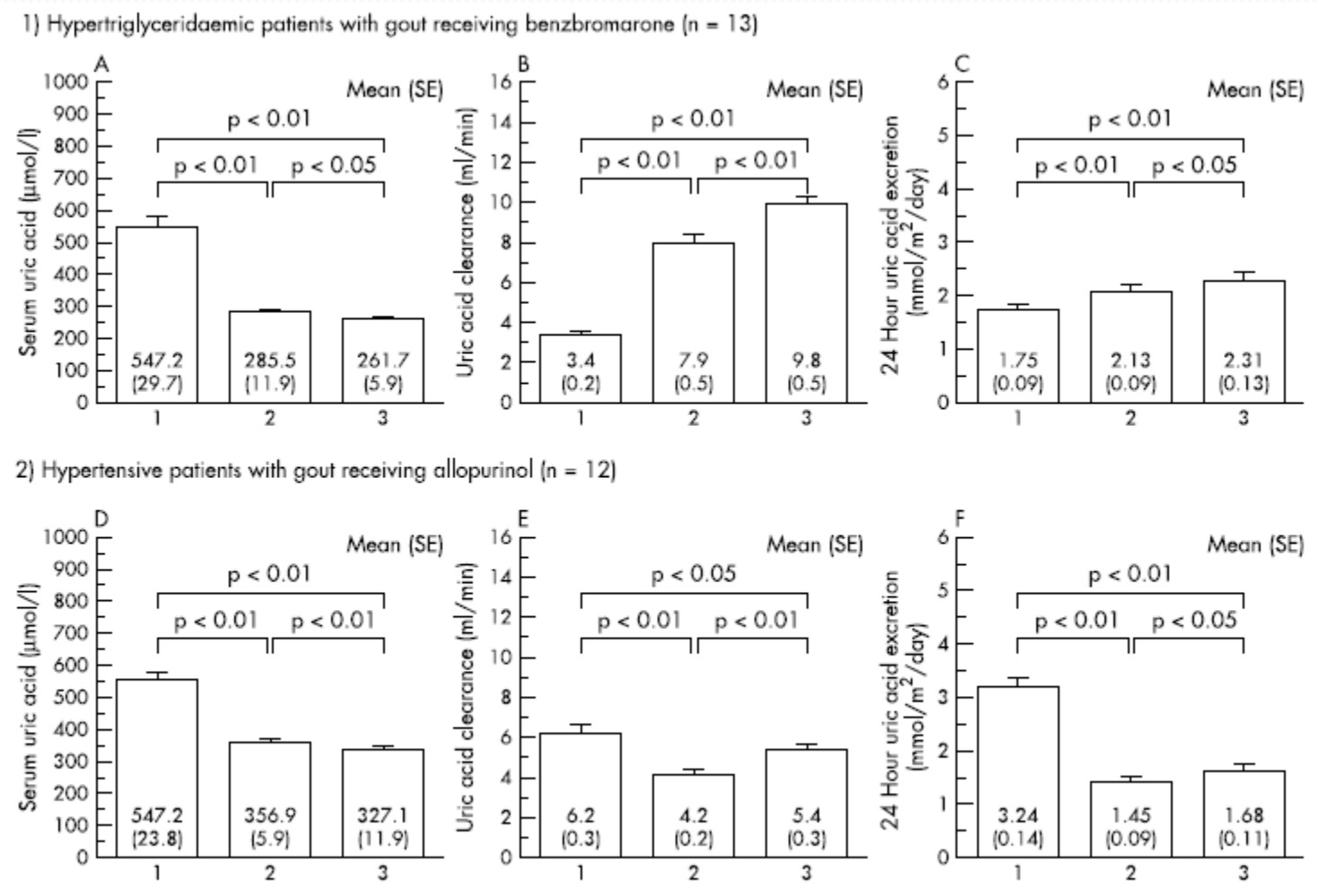


Kidney International, Vol. 56 (99), pp. 1879–1885

- Efecto uricosúrico de Losartán es individual y no es un efecto de clase:
  - Effect of valsartan on renal handling of uric acid in healthy subjects. *J Nephrol. 2000 Mar =Apr;13(2):126-8*.
  - Comparative effects of losartan and irbesartan on serum uric acid in hypertensive patients with hyperuricaemia and gout. *J Hypertens. 2001 Oct;19(10):1855-60.*
  - Effect of losartan versus candesartan on uric acid, renal function, and fibrinogen in patients with hypertension and hyperuricemia associated with diuretics. *Am J Hypertens. 2006 Feb;19(2):208-13*
  - Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens. 1999 Jul;17(7):1033-9.*

Effects of combination treatment using anti-hyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism

S Takahashi, Y Moriwaki, T Yamamoto, Z Tsutsumi, T Ka, M Fukuchi



Ann Rheum Dis 2003;**62**:572–575

Febuxostat, a Novel Nonpurine Selective Inhibitor of Xanthine Oxidase

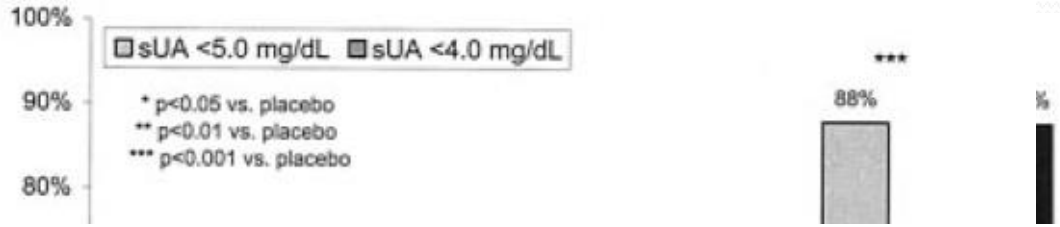
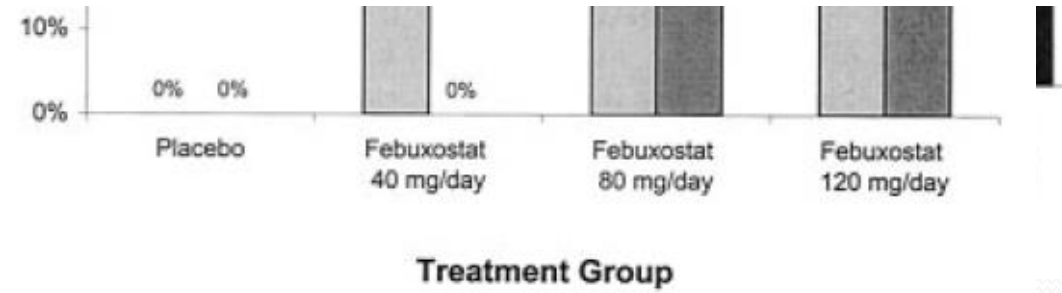


Table 3. Incidence of most frequent treatment-related adverse events*

Adverse event	Placebo (n = 38)	Febuxostat 40 mg/day (n = 37)	Febuxostat 80 mg/day (n = 40)	Febuxostat 120 mg/day (n = 38)
Abdominal pain	5	3	3	3
Diarrhea	8	0	10	8
Abnormal results of liver function tests	0	5	3	3

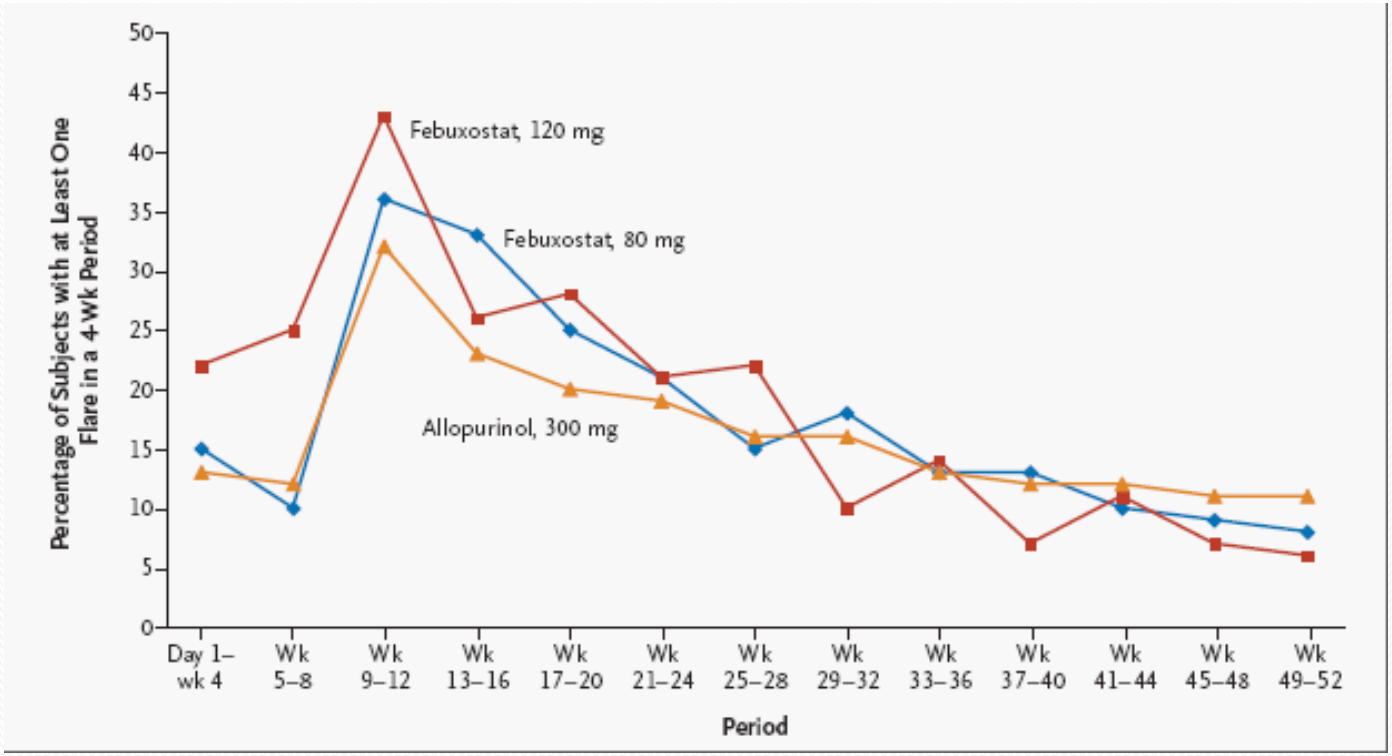
* Adverse events reported by at least 2 subjects in any treatment group. Values are percentages.



ARTHRITIS & RHEUMATISM
Vol. 52, No. 3, March 2005, pp 916–923

Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout

Michael A. Becker, M.D., H. Ralph Schumacher, Jr., M.D., Robert L. Wortmann, M.D., Patricia A. MacDonald, B.S.N., N.P., Denise Eustace, B.A., William A. Palo, M.S., Janet Streit, M.S., and Nancy Joseph-Ridge, M.D.



N Engl J Med 2005;353:2450-61.