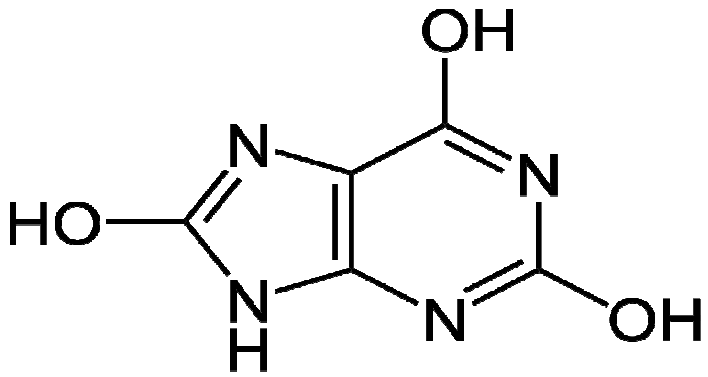
Patients avec HTA et/ou maladie rénale chronique: traiter l' hyperuricémie assympômatique ?



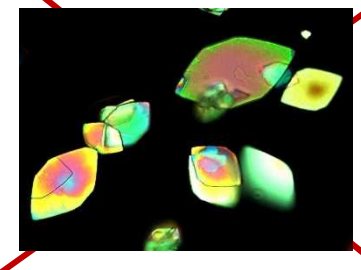
Patrick Saudan
Service de Néphrologie, Département des Spécialités Médicales, HUG

Hôpitaux Universitaires Genève

Acide urique et système rénal

~~Goutte~~ et IRC

Néphropathies aiguë ~~ou~~ chroniques uratiques



Hyperuricémie assymptomatique , HTN et IRC

Aspects bénéfiques acide urique chez l'homme ?

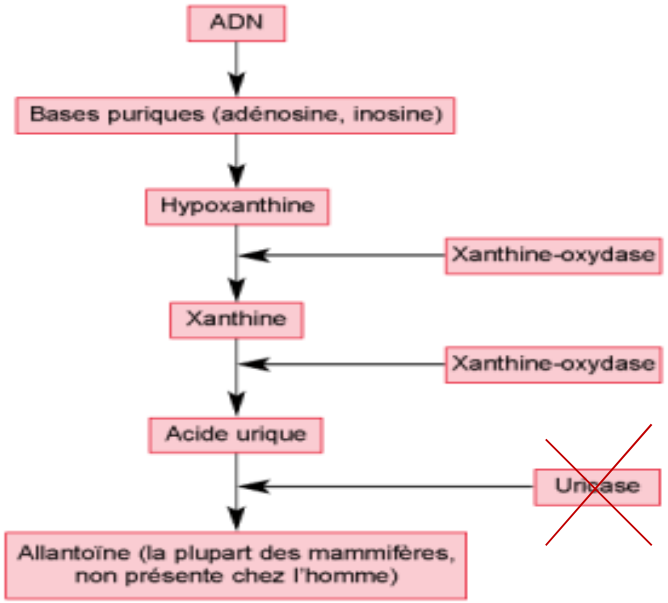


Figure 1. Métabolisme des purines

- Puissant antioxydant
- Activation syst RAA en condition de déprivation sodique
- Taux sériques plus élevés chez l'espèce humaine

  ↓

  avantage pour longévité espèce humaine ?

Hadjeres et al RMS 2009, Hediger MA et al. Physiology 2005

Effet protecteur acide urique sur maladies neuro-dégénératives ?

Clinical associations between gout and multiple sclerosis, Parkinson's disease and motor neuron disease: record-linkage studies

Julia Pakpoor[1], Olena O Seminog[1], Sreeram V Ramagopalan[2] and Michael J Goldacre[1*]

Pakpoor *et al. BMC Neurology* (2015) 15:16
DOI 10.1186/s12883-015-0273-9

Serum Urate and the Risk of Parkinson's Disease: Results From a Meta-Analysis

Chunhong Shen, Yi Guo, Wei Luo, Chen Lin, Meiping Ding

Can J Neurol Sci. 2013; 40: 73-79

Homéostasie acide urique chez l'homme

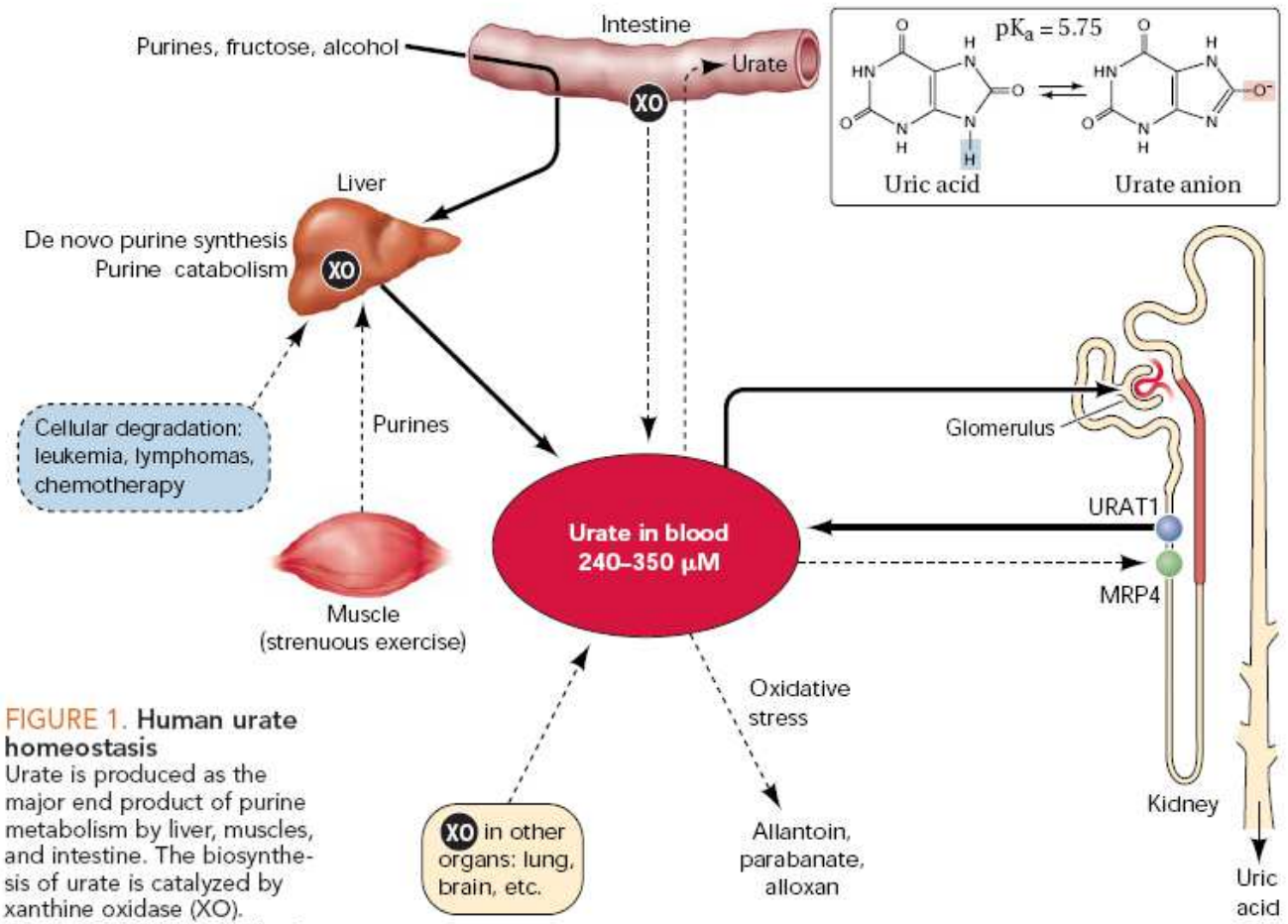
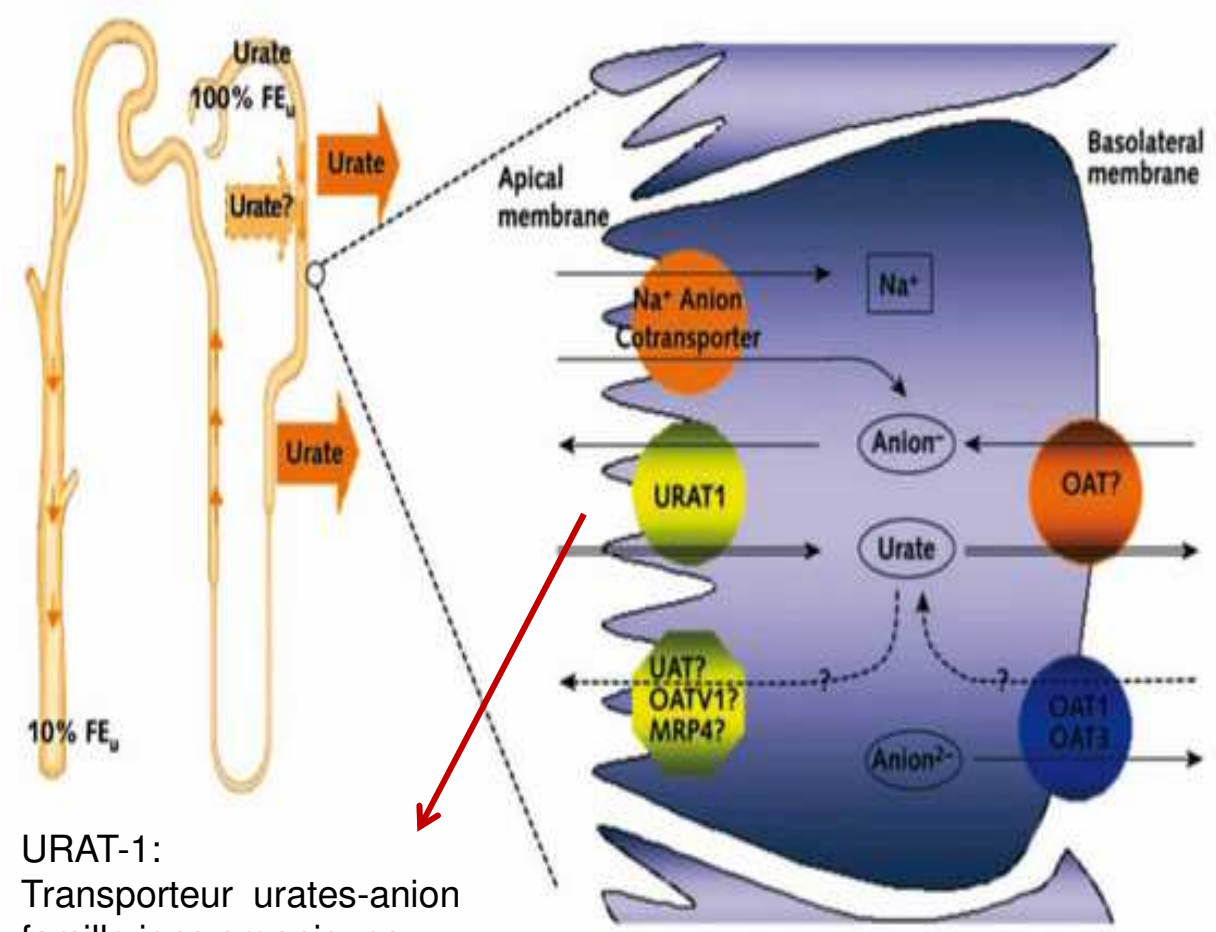


FIGURE 1. **Human urate homeostasis**
Urate is produced as the major end product of purine metabolism by liver, muscles, and intestine. The biosynthesis of urate is catalyzed by xanthine oxidase (XO). Approximately two thirds of the daily turnover of urate is accounted for by urinary excretion, with the remaining one third being excreted into the gut as feces. In the human kidney, filtered urate is reabsorbed via the transporter URAT1. To a lesser extent, urate may also be secreted directly into the tubular lumen via the MRP4 pump. Dietary fructose, alcohol consumption, and cellular degradation can furthermore increase urate levels (see text for details). The production allantoin and related compounds may occur in tissues, such as vascular smooth muscle cells, as a result of nonenzymatic reactions of urate with reactive oxygen species (13).

Hediger MA et al. Physiology 2005

Hôpitaux Universitaires Genève

Acide urique et fonction rénale



URAT-1:
Transporteur urates-anion
famille ions organiques
555 aa
12 domaines stransmembranaires

Johnson et al, AJKD 2013

Urates filtrés puis réabsorbés
(et aussi sécrétés)

Causes classiques
hyperuricémie
en aigü:
-Hypovolémie

en chronique:
-Diurétiques
- IRC (baisse filtration glomérulaire, compétition avec d'autres anions sur le transporteur MPR4)

Hôpitaux Universitaires Genève

Effet des anti-HTA sur le taux sérique d'acide urique

-Effet direct des diurétiques via augmentation réabsorption AU
-Effet indirect via réabsorption accrue Na ds tube proximal liée à « hypovolémie induite » par diurétiques

Tableau 2. Effet des antihypertenseurs sur le taux sérique d'acide urique
Effets des différents anti-hypertenseurs et de leur association sur le taux sérique d'acide urique.
Abréviations : AU = taux sérique d'acide urique, IEC = inhibiteurs de l'enzyme de conversion.

Anti-hypertenseurs	Effet sur le taux sérique d'acide urique	Commentaires
Diurétiques	↑↑	Effet en quelques jours, réversible à l'arrêt du traitement
Inhibiteurs de l'enzyme de conversion (IEC)	→ ou ↓	Diminuent l'AU de façon modérée (environ 10%)
IEC + diurétiques	↑	L'association provoque une élévation modérée du SUA
Antagonistes de l'angiotensine II	→	Pas d'effet sur le SUA
Losartan (Cosaar®)	↓↓	Le losartan est le seul antagoniste qui diminue efficacement le SUA (-30%)
Losartan + diurétiques	→	Le losartan contrecarre l'effet des diurétiques
Antagonistes du calcium	→ ou ↓	Tester pour l'amlodipine et le diltiazem Effet modéré (10%)
Béta-bloquants	→ ou ↑	Effet modeste (5-10%)
Béta-bloquants + diurétiques	↑↑	L'association augmente l'AU

Deleaval , RMS 2005, UptoDate 2017

Epidémiologie hyperuricémie

Etude NHANES 2007-2008:
Prévalence goutte aux US: H 5.9 % F 2%
Prévalence hyperuricémie assmptomatique :
H 21.2 % F 21.6%

Zhou et al. Arthritis Rheumatism 2011

THE PROBLEM: SUGARY DRINKS ARE A MAJOR CONTRIBUTOR TO THE OBESITY EPIDEMIC

Harvard School of Public Health 2012

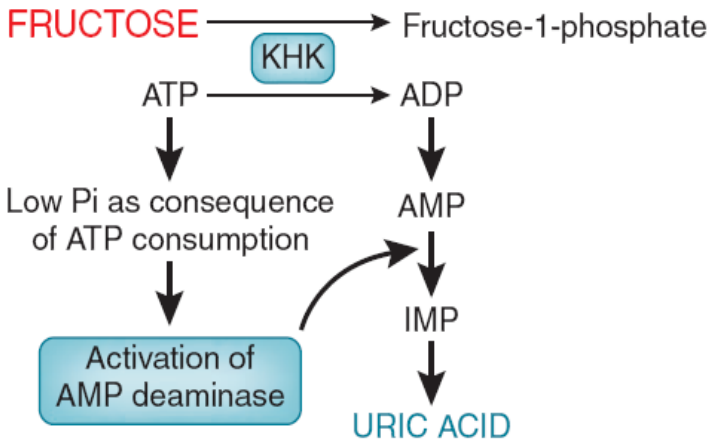


Figure 1. A pathway by which fructose is metabolized into uric acid. KHK, keto-hexokinase.

Johnson et al. JASN 2010

Acide urique et HTN, IRC: marqueur d'association ou facteur de progression ?

Première hypothèse d'un lien acide urique-HTN-maladie rénale

ON CHRONIC BRIGHT'S DISEASE, AND ITS ESSENTIAL SYMPTOMS.
BY F. A. MAHOMED, M.D., MEDICAL REGISTRAR TO GUY'S HOSPITAL, AND ASSISTANT-PHYSICIAN TO THE LONDON FEVER HOSPITAL.
Lancet 1879 1: 399-401

120 ans plus tard

6763 Framingham Heart Study participants (mean age, 47 years).

CONCLUSIONS:
These findings indicate that uric acid does not have a causal role in the development of coronary heart disease, death from cardiovascular disease, or death from all causes. Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.

Culleton et al. Arch Int Med 1999

Hôpitaux Universitaires Genève

Acide urique et HTN, IRC: marqueur d'association ou facteur de progression ?

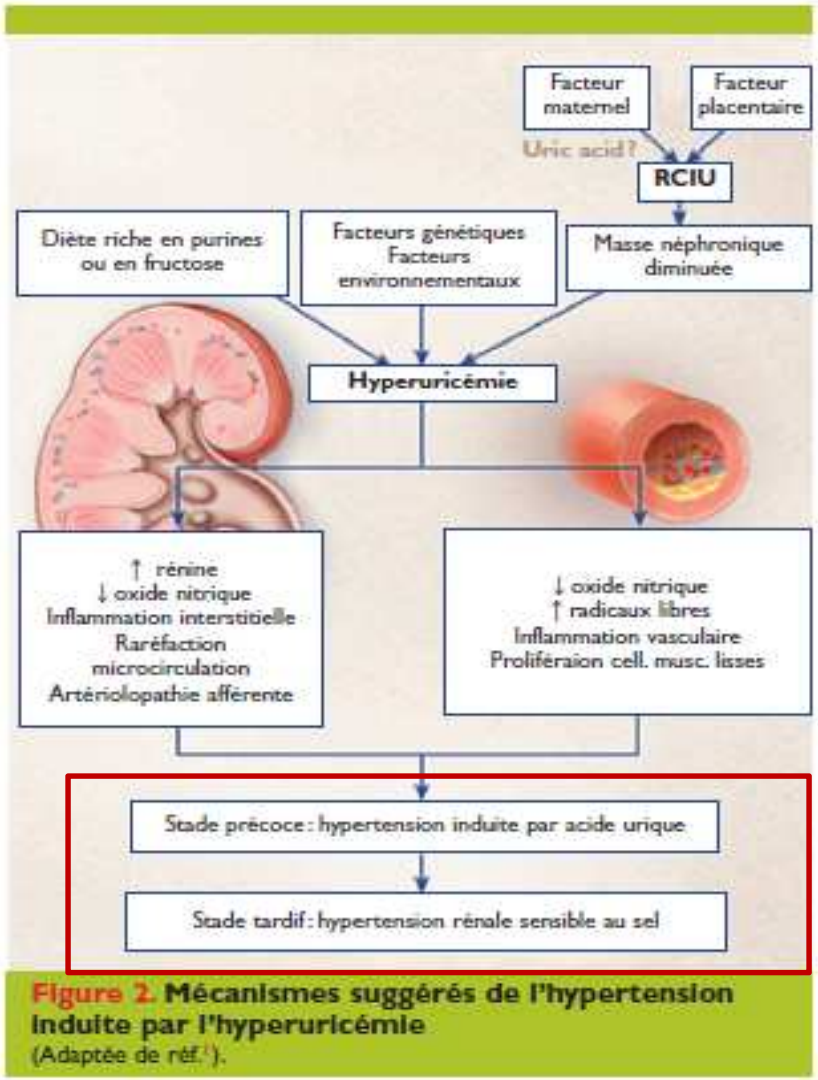


Figure 2. Mécanismes suggérés de l'hypertension induite par l'hyperuricémie
(Adaptée de réf.[1]).

AU induit une dysfonction endothéliale:
AU inhibe la production NO
AU augment prolif cellulaire et production cytokines
AU stimule directement le système Rénine-Angiotensine

Hadjeres et al. RMS 2009 Feig et al. NEJM 2008

Acide urique et HTN: études observationnelles

Table 1. Epidemiology of uric acid and hypertension

First author	Year	Patients	Risk of hypertension	Ref.
Kahn	1972	10000 Israeli men, age 17–25 enrolled at military induction	2-fold risk at 5 years	[35]
Fessel	1973	224 white males in Western US, age > 35 years	Greater increase in SBP at 4 years	[36]
Gruskin	1985	55 adolescents, racially mixed US population	Higher uric acid, higher BP	[37]
Rovda	1985	145 Caucasian children in Moscow, age 8–17	Uric acid > 8mg/dl predicts severe	[38]
Brand	1986	4286 men and women age 35–50 in the Framingham cohort	Uric acid, SBP rise a linear relation	[39]
Torok	1990	17643 Hungarian children, age 6–19	Uric acid predicts adolescent hypertension	[40]
Selby	1990	2062 adult men and women in the Kaiser Permanente, Multiphasic Health Checkup cohort in Northern California	2-fold risk at 6 years	[41]
Hunt	1991	1482 adult men and women in 98 Utah pedigrees	2-fold risk at 7 years	[42]
Goldstein	1993	6768 healthy children age 6–17	Uric acid predicts adolescent hypertension	[43]
Jossa	1994	619 adult males from Southern Italy	2-fold risk at 10 years	[44]
Dyer	1999	5115 black men and women age 18–30	Increased risk at 10 yrs	[45]
Taniguchi	2001	6356 Japanese men age 35–60	2-fold risk at 10 years	[46]
Imazu	2001	140 Japanese American males age 40–69	3.5-fold risk at 15 years	[47]
Feig	2003	175 racially diverse children, age 6–18 in Texas	Uric acid > 5.5mg/dl predicts hypertension	[48]
Masuo	2003	433 nonobese Japanese men age 18–40	Increase 1 mg/dl associated with 27 mm Hg rise in SBP at 5 years	[49]
Nakanishi	2003	Male office workers in Japan, age 35–59	1.6-fold risk at 6 years	[50]
Nagahama	2004	4489 Japanese men and women, age > 30	1.7 fold risk at 13 years	[51]
Alper	2005	577 black (58%) and white (42%) children enrolled at age followed until age 18–35, Bogalusa Trial	Increased risk of diastolic htn at 11 years	[52]
Sundstrom	2005	3329 men and women in the Framingham cohort	1.6-fold risk at 4 years	[53]
Perlstein	2006	2062 healthy men age 40–60 at enrollment	1.5-fold risk at 21 years	[54]
Mellen	2006	9104 mixed race (black and white) men and women age 45–64 yrs at enrollment, ARIC Trial	1.5-fold risk at 9 years	[55]
Shankar	2006	2 520 White men (44%) and women (56%) age 43–84 in Wisconsin	1.65-fold risk at 10 years	[56]
Forman	2006	750, mostly white men in Massechussetts, Health Professionals Follow Up Study	1.1-fold risk at 8 years	[57]
Krishnan	2007	3073 men age 35–57 yrs, MRFIT Study	1.8-fold at 6 years	[58]
Forman	2009	1496 women, racially diverse, age 32–52, Nurse's Health Study	1.9-fold at 6 years	[59]
Zhang	2009	7220 men (74%) and women (26%) in Quingdoa China, mean age 37	1.39-fold for men and 1.85-fold for women at 4 years	[60]
Jones	2009	141 children age 7–18, 64% male, 71% black	2.1-fold risk in adolescence	[61]

Table 1 (*Continued*)

First author	Year	Patients	Risk of hypertension	Ref.
Leite	2010	1410 men and women in Milan, Italy, young cohort 42–59, older cohort 60–74	Increased risk in middle age but not elderly patients	[62]
Grayson	2010	55607 adults, meta-analysis of 18 prospective studies	1.4-fold risk for each 1mg/dl increase in uric acid	[63]
Silverstein	2011	108 racially diverse children, age 6–18 in Texas and Washington, DC	Linear association between uric acid and SBP in children on dialysis	[18]
Jolly	2012	1078 Alaskan native Americans with CKD IHI	1.2-fold age adjusted risk	[64]
Loeffler	2012	6036 adolescents, age 11–17 evaluated in NHANES	2.03-fold risk if serum uric acid > 5.5mg/dl	[65]
Bao	2013	11119 healthy adults without hypertension	Higher uric acid associated with 1.25-fold risk of prehypertension	[66]
Emokpae	2013	351 patients with essential hypertension, 100 healthy controls in Nigeria	Serum uric acid correlated with systolic and diastolic BP	[67]
Turak	2013	112 hypertensive patients, 50 normotensive controls	Higher uric acid associated with nondipping status on ambulatory blood pressure	[68¶]
Viazzi	2013	501 Italian children referred for CV risk assessment	Uric acid independently predicted higher BP	[69]

Environ 40 études observationnelles sur 40 ans avec conclusion univoques:
-Hyperuricémie associée avec HTN
-Hyperuricémie précède l'HTN

Acide urique et IRC: études observationnelles

Table 2. Epidemiology of uric acid and chronic kidney disease

First author	Year	Patients	Major findings	Ref.
Iseki	2001	6403, Okinawa General Health	Uric acid > 8 mg/dl increase CKD risk 3-fold in men and 10-fold in women	[78]
Domrongkitchaipron	2005	3499 Healthy individuals in SE Asia followed for 12 years	Uric acid > 6.3 associated with 1.69-fold risk of progressive decline in renal function	[79]
Chonchol	2007	5808, Cardiovascular Health Study	Uric acid strongly associated with prevalent but weakly with incident CKD	[80]
Obermayr	2008	21 457 Vienna Health Screening Project	Uric acid > 7 mg/dL increased risk of CKD 1.74-fold in men, 3.12-fold in women	[81]
Sturm	2008	227, MMKD Study	Uric acid predicted progression of CKD only in unadjusted sample	[82]
Weiner	2008	13 338, ARIC	Each 1 mg/dl increase in uric acid increase risk of CKD 7–11%	[83]
Borges	2009	385 Hypertensive women	Elevated uric acid associated with 2.63-fold increased risk of CKD in hypertensive women	[84]
Chen, N	2009	2596, Ruijin Hospital, China	Linear correlation between uric acid and degree of CKD	[85]
Chen, Y	2009	5722, Taipei University Hospital	Uric acid associated with prevalent CKD in elderly	[86]
Hsu	2009	177 570, USRDS	Higher uric acid quartile conferred 2.14-fold increased risk of ESRD over 25 years	[87]
Madero	2009	840, Instituto Nacional de Cariologia, Mexico	Patients with CKD 3–4 and uric acid correlates with death but not to ESRD	[88]
Park	2009	134, Yonsei University	Uric acid > 7 mg/dl correlates with more rapid decline in residual renal function in peritoneal dialysis patients	[89]
See	2009	28 745, Chang Gung University	Uric acid > 7.7 mg/dl in men and > 6.6 mg/dl in women only weakly associated with prevalent renal impairment	[90]
Bellomo	2010	900 healthy blood donors, prospective study	Each 1 mg/dl increase in serum uric acid correlates with 28% increased risk of reduced GFR in 5 years	[91]
Ben Dov	2011	2449 healthy adults followed for 25 years in the Jerusalem Lipid Research Clinic	Uric acid > 6.5 mg/dl in men, > 5.3 mg/dl in women associated with 2.1-fold increased risk of CKD	[92]
Dawson	2013	6984 adults in Glasgow Blood Pressure Clinic	Highest quartile of serum uric acid associated with GFR decline and increased all cause mortality	[93]
Helal	2013	680 patients with Autosomal Dominant Polycystic Kidney Disease	Higher quartiles of uric acid associated with more rapid decline in renal function	[94•]
Iseki	2013	16 630 healthy adults in Okinawa, followed over 10 years	Increased uric acid, within normal range predicts decline in GFR over 10 years	[95•]
Krishnan	2013	2116 patients without kidney disease in Veteran Administration, mean age 63	Higher serum uric acid predicts new onset kidney disease	[96•]
Oh	2013	1743 healthy Korean men without proteinuria	Highest tertile of uric acid had 2.3-fold risk of proteinuria over 5 years	[97•]
Ohta	2013	104 hypertensive patients	Serum uric acid had linear negative correlation with eGFR over 10 years	[98•]

Environ 21 études observationnelles sur 22 ans avec conclusion univoques:
-Hyperuricémie associée avec IRC
-Hyperuricémie précède l'IRC

HUG Hôpitaux Universitaires Genève

Acide urique et IRC: études observationnelles

21475 volontaires sains
7,5 ans de suivi
AU 415-430 risque doublé d'avoir GFR < 60 ml/mn
AU > 535 risque triplé

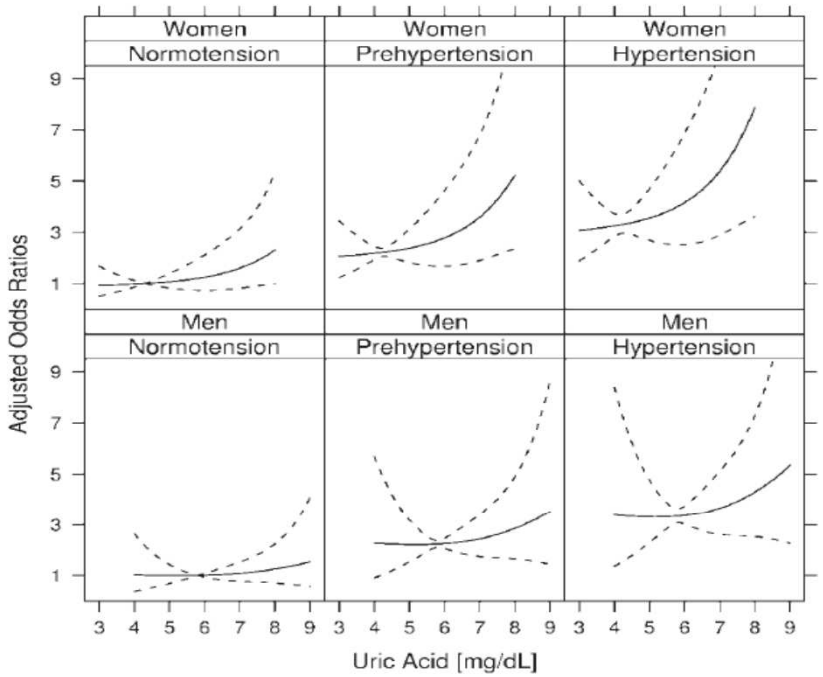


Figure 2. OR for development of a GFR <60 ml/min per 1.73 m^2 depending on UA levels (natural cubic splines) compared with mean UA levels (4.2 mg/dl for women and 5.9 mg/dl for men); stratified for gender and hypertension groups[23] adjusted for GFRb, age, waist circumference, fasting glucose (natural cubic spline), HDL (log-transformed), triglycerides (log-transformed), and antihypertensive drug use. Dashed lines denote 95% CI. Hypertension groups: normal BP, systolic <120 mmHg and diastolic <80 mmHg; prehypertension, systolic 120 to 139 mmHg or diastolic 80 to 89 mmHg; hypertension, systolic ≥140 mmHg or diastolic ≥90 mmHg.[23]

Obermayr et al. JASN 2008

Traitement hyperuricémie et HTN, IRC: fort peu d'études interventionnelles

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

American Journal of Kidney Diseases, Vol 47, No 1 (January), 2006: pp 51-59

Allopurinol:progression IRC ralentie
RCT, 54 patients, dose100-200 mg/j

Effect of Allopurinol on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension: A Randomized Trial

Daniel I. Feig; Beth Soletsky; Richard J. Johnson

JAMA. 2008;300(8):924-932 (doi:10.1001/jama.300.8.924)

Allopurinol: Baisse HTA
chez adolescents hypertendus
dose200 mg/j

Effect of Allopurinol in Chronic Kidney Disease Progression and Cardiovascular Risk

Marian Goicoechea, Soledad García de Vinuesa, Ursula Verdalles, Caridad Ruiz-Caro, Jara Ampuero, Abraham Rincón, David Arroyo, and José Luño

Servicio de Nefrología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Clin J Am Soc Nephrol 5: 1388–1393, 2010.

Allopurinol:Progression IRC ralentie
113 patients randomisés
allopurinol 100 mg/j vs placebo

Allopurinol Benefits Left Ventricular Mass and Endothelial Dysfunction in Chronic Kidney Disease

Michelle P. Kao,* Donald S. Ang,* Stephen J. Gandy,† M. Adnan Nadir,* J. Graeme Houston,† Chim C. Lang,* and Allan D. Struthers*

J Am Soc Nephrol 22: 1382–1389, 2011

Allopurinol: diminution LVH
et dysfonction endothéliale a 9 mois.
0 effet sur GFR

Traitement hyperuricémie et HTN, IRC: fort peu d'études interventionnelles

A Randomized Study of Allopurinol on Endothelial Function and Estimated Glomular Filtration Rate in Asymptomatic Hyperuricemic Subjects with Normal Renal Function

Mehmet Kanbay, Bulent Huddam,† Alper Azak,† Yalcin Solak,‡ Gulay Kocak Kadioglu,† Ismail Kirbas,§ Murat Duranay,† Adrian Covic,‖ and Richard J. Johnson¶*

Clin J Am Soc Nephrol 6: 1887–1894, 2011.

Allopurinol: amélioration dysfonction endothéliale
TA syst,GFR chez 30 patients hyperuricémiques

Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial

Goicoechea et al. Am J Kidney Dis 2015

Allopurinol: Maintien ralentissement IRC progression et diminution événements CV

Vascular Function and Uric Acid-Lowering in Stage 3 CKD

Diana I. Jalal,* Emily Decker,* Loni Perrenoud,* Kristen L. Nowak,* Nina Bispham,† Tapan Mehta,* Gerard Smits,* Zhiying You,* Douglas Seals,† Michel Chonchol,* and Richard J. Johnson*

*Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; and †Department of Integrative Physiology, University of Colorado Boulder, Boulder, Colorado

JASN2016

Allopurinol: absence d'amélioration dysfonction endothéliale et pas d'effet sur GFR !

Effect of Uric Acid Lowering on Renin-Angiotensin-System Activation and Ambulatory BP: A Randomized Controlled Trial

Ciaran J. McMullan,† Lea Borgi,*† Naomi Fisher,‡ Gary Curhan,*† and John Forman*†*

CJASN in press

Allopurinol: pas de baisse HTA chez patients hyperuricémiques !

Hôpitaux Universitaires Genève

Traitement hyperuricémie et HTN, IRC: fort peu d'études interventionnelles

Meta-analyse: outcomes progression IRC et action protéinurie

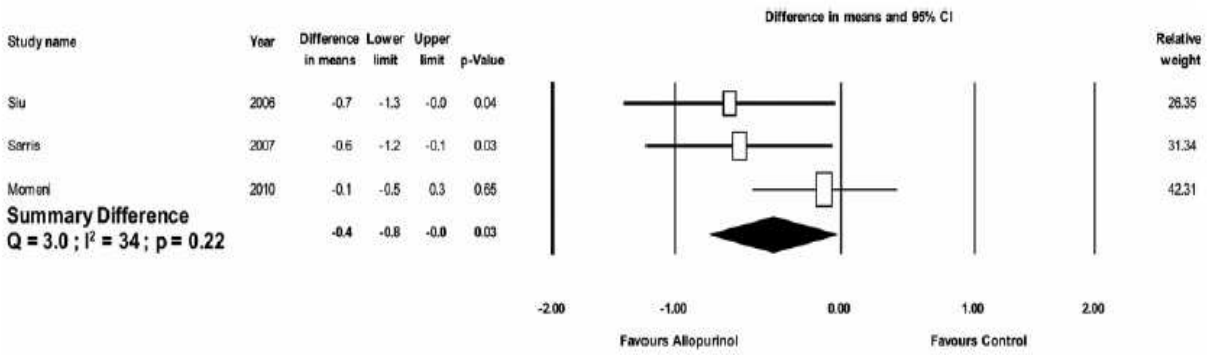


FIGURE 4: Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in serum creatinine concentration (mg/dL) from baseline. To convert creatinine from mg/dL to μmol/L, multiply by 88.4.

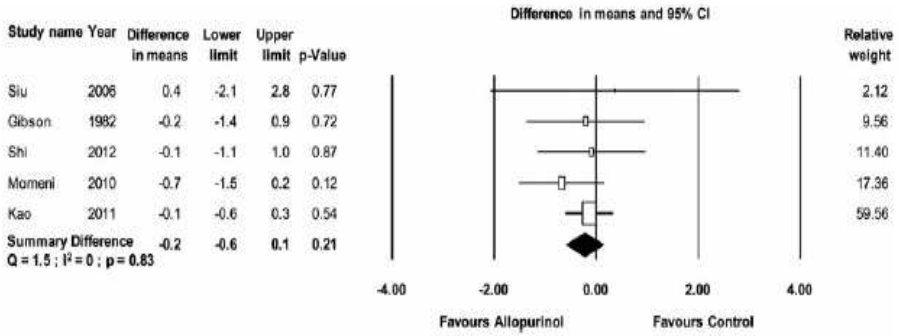


FIGURE 5: Forest plot showing the effect of uric acid-lowering therapy compared with placebo or no treatment on change in proteinuria (g/day) from baseline.

Beaucoup d'hétérogénéité dans les études résultats à considérer avec prudence

Bose et al. NDT 2014

Acide urique et IRC: études interventionnelles

Allopurinol and Progression of CKD and Cardiovascular Events: Long-term Follow-up of a Randomized Clinical Trial

Marian Goicoechea, MD, PhD, Soledad Garcia de Vinuesa, MD, Ursula Verdalles, MD, Eduardo Verde, MD, Nicolas Macias, MD, Alba Santos, MD, Ana Pérez de Jose, MD, PhD, Santiago Cedeño, MD, Tania Linares, MD, and Jose Luño, MD, PhD

Suivi à 7 ans 113 patients
Allopurinol 100 mg/j vs placebo
pdt les premiers 24 mois
Patients avec 71ans d'âge moy,
Taux d'acide urique moy: 450
GFR: 40 ml/mn

Table 1. Baseline Characteristics

	Control (n = 56)	Allopurinol (n = 57)
Age (y)	71.4 ± 9.5	72.1 ± 7.9
Cystatin C (mg/L)	1.9 ± 0.7	1.9 ± 0.5
Serum creatinine (mg/dL)	1.8 ± 0.6	1.7 ± 0.4
eGFR (mL/min/1.73 m^2)	39.5 ± 12.4	40.6 ± 11.3
Uric acid (mg/dL)	7.3 ± 1.6	7.8 ± 2.1
hs-CRP (mg/L)	3.4 [1.8-7.0]	4.4 [2.5-7.0]
Serum fibrinogen (mg/dL)	374 ± 78	381 ± 79
ESR (mm/h)	15 [8-29]	17 [8-32]
Hemoglobin (g/dL)	14.5 ± 4.6	13.6 ± 1.7
Serum albumin (g/dL)	4.4 ± 0.3	4.3 ± 0.3
Albuminuria (mg/d)	35 [11-436]	36 [15-356]
Renal pathology		
Diabetes mellitus	10 (18)	9 (16)
Hypertensive kidney disease	25 (45)	28 (49)
Glomerulonephritis	5 (9)	1 (2)
Polycystic kidney disease	1 (2)	2 (3)
Interstitial nephropathy	2 (3)	8 (14)
Systemic vasculitis	2 (3)	0 (0)
Unknown-cause kidney disease	11 (20)	9 (16)
Diabetes mellitus	20 (36)	22 (39)
Ischemic cardiopathy	10 (18)	16 (28)
Cerebrovascular disease	2 (4)	2 (3)
Peripheral vascular disease	1 (2)	5 (9)
Diuretic use	30 (54)	36 (63)
Thiazide diuretics	13 (23)	15 (27)
Loop diuretics	17 (30)	21 (37)
RAAS blockers	41 (73)	47 (82)
Calcium channel blockers	20 (36)	13 (23)
Statin treatment	24 (43)	27 (47)
Antiplatelet treatment	18 (32)	15 (26)
Double treatment	28 (50)	32 (56)
Triple treatment	11 (20)	8 (14)

AJKD 2015

Acide urique et IRC: études interventionnelles

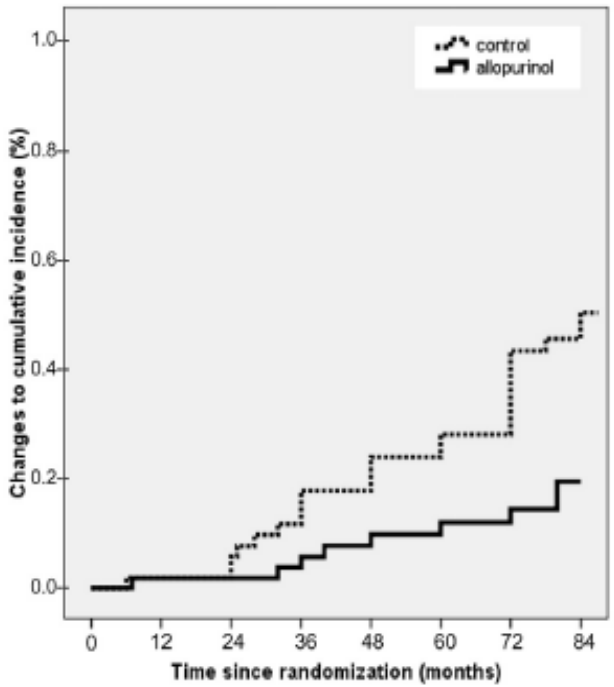
Allopurinol and Progression of CKD and Cardiovascular Events: Long-term Follow-up of a Randomized Clinical Trial

Marian Goicoechea, MD, PhD, Soledad Garcia de Vinuesa, MD, Ursula Verdalles, MD, Eduardo Verde, MD, Nicolas Macias, MD, Alba Santos, MD, Ana Pérez de Jose, MD, PhD, Santiago Cedeño, MD, Tania Linares, MD, and Jose Luño, MD, PhD

Baisse de eGFR à 84 mois:
-6.5 + 1.6 ml/mnl (Allop.)
--13.3 + 5mL/mn (Placebo)

« Evénements » rénaux:
16% groupe allopurinol
47% groupe placebo
(HR 0.32, 95% CI 0.15-0.69, p=0.004)

« Evénements» CV: 16 (A) vs 23 (Pl.)
(HR 0.43; 95% CI 0.23-0.88, p= 0.02)



Time (mo)	0	12	24	36	48	60	72	84
Allopurinol (n)	57	55	54	46	41	37	35	32
Control (n)	56	52	49	41	37	34	27	21

AJKD 2015

Hôpitaux Universitaires Genève

Acide urique et HTN: études interventionnelles

Vascular Function and Uric Acid-Lowering in Stage 3 CKD

Diana I. Jalal,* Emily Decker,* Loni Perrenoud,* Kristen L. Nowak,* Nina Bispham,† Tapan Mehta,* Gerard Smits,* Zhiying You,* Douglas Seals,† Michel Chonchol,* and Richard J. Johnson*

*Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado; and †Department of Integrative Physiology, University of Colorado Boulder, Boulder, Colorado

80 patients avec hyperuricémie assymptomatique (env 500 µmol/L) et IRC
Randomisés allopurinol (300 mg/j) durant 12 semaines ou placebo

Table 2. Change from baseline according to treatment group

Variable	Placebo (*n*=41)	Allopurinol (*n*=39)	*P* Value
Serum urate, mg/dl	0.05±1.54	−3.24±1.35	<0.001
BA-FMD, % Δ	0.2±4.1	0.9±3.9	0.47
NMD, % Δ	−1.3±5.3	0.9±6.1	0.14
Systolic BP, mmHg	−1.63±15.51	−1.70±17.52	0.85
Diastolic BP, mmHg	−0.97±11.8	0.97±10.8	0.51
CRP, mg/L	0.70±3.4	0.42±9.5	0.78
IL-6, pg/ml	0.15±3.1	0.37±2.7	0.75
MCP-1, pg/ml	−4.7±45.8	3.6±36.7	0.47
Ox-LDL, U/L	−0.08±11.8	−2.97±16.4	0.19

Value are expressed as absolute change from baseline±SD. BA-FMD % Δ, % change in BA-FMD; NMD % Δ, % change in NMD.

Pas d'effet sur fonction endothéliale, paramètres inflammatoires, PA.
Tendance à amélioration chez non-diabétiques (non statist. significative mais trop petit collectif)

JASN 2017

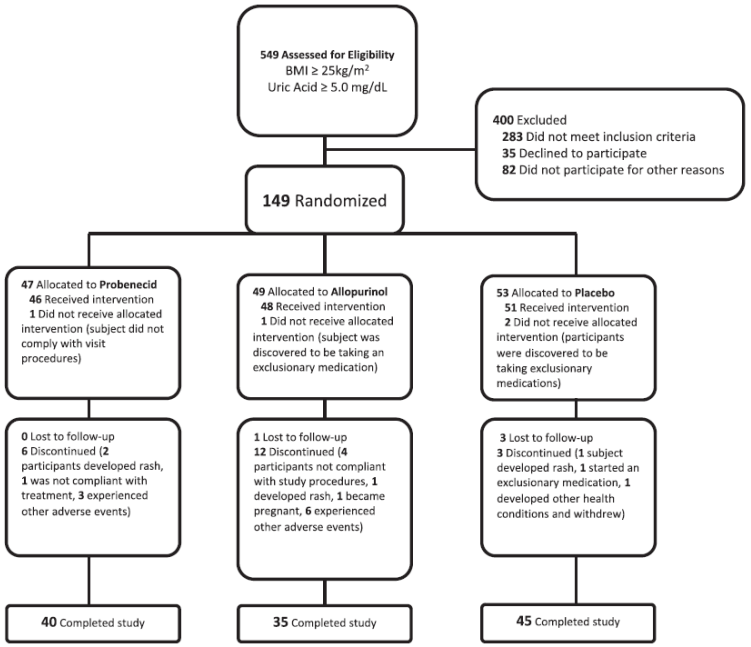
Acide urique et HTN: études interventionnelles

Effect of Uric Acid Lowering on Renin-Angiotensin-System Activation and Ambulatory BP: A Randomized Controlled Trial

Ciaran J. McMullan,*† Lea Borgi,*† Naomi Fisher,‡ Gary Curhan,*† and John Forman*†

Design, setting, participants, & measurements In a double-blind placebo-controlled trial conducted from 2011 to 2015, we randomly assigned 149 overweight or obese adults with serum uric acid ≥5.0 mg/dl to uric acid lowering with either probenecid or allopurinol, or to placebo. The primary endpoints were kidney-specific and systemic RAS activity. Secondary endpoints included mean 24-hour systolic BP, mean awake and asleep BP, and nocturnal dipping.

Diabétiques et hypertendus exclus !



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Hôpitaux Universitaires Genève

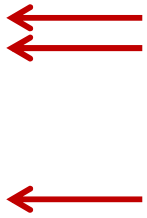
Acide urique et HTN: études interventionnelles

Effect of Uric Acid Lowering on Renin-Angiotensin-System Activation and Ambulatory BP: A Randomized Controlled Trial

Table 1. Baseline characteristics of all randomized participants

Characteristic	Probenecid (n=47)	Allopurinol (n=49)	Placebo (n=53)
Mean age (SD), yr	37(14)	43(13)	41(14)
Men, n (%)	24 (51.1)	25 (51.0)	25 (47.2)
White, n (%)	27 (57.5)	32 (65.3)	33 (62.3)
Clinical measures			
Mean serum uric acid (SD), mg/dl	6.1 (1.1)	6.1 (0.9)	6.1 (0.8)
Mean body mass index (SD), kg/m^2	33.4(6.6)	35.7(6.3)	33(5.9)
Mean eGFR[a] (SD), ml/min per 1.73 m^2	102 (18)	99 (17)	102 (18)
Mean serum creatinine (SD), mg/dl	0.9 (0.2)	0.9 (0.1)	0.9 (0.1)
Mean serum ALT (SD), IU/L	20.7 (9.5)	18.5 (8.0)	19.0 (7.8)
Mean serum AST (SD), IU/L	18.9 (5.5)	17.8 (6.0)	16.8 (3.4)
Mean systolic BP (SD), mmHg	119 (11)	119 (12)	119 (10)
Mean diastolic BP (SD), mmHg	77 (7)	78 (8)	78 (7)

ALT, Alanine Transaminase; AST, Aspartate Transaminase.
[a]eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.



CJASN in press

Acide urique et HTN: études interventionnelles

Effect of Uric Acid Lowering on Renin-Angiotensin-System Activation and Ambulatory BP: A Randomized Controlled Trial

Ciaran J. McMullan,*† Lea Borgi,*† Naomi Fisher,‡ Gary Curhan,*† and John Forman*†

Resultats:

-Baisse marquée acide urique avec allopurinol et probénécide

-pas d'effet sur système RAA

-pas de baisse significative PA Syst sur 24h avec allopurinol ou probenecide

Conclusions In contrast to animal experiments and observational studies, this randomized, placebo-controlled trial found that uric acid lowering had no effect on kidney-specific or systemic RAS activity after 8 weeks or on mean systolic BP. These data do not support the hypothesis that higher levels of uric acid are a reversible risk factor for increased BP.

CJASN in press

Traitements hypouricémiants : effets secondaires

Table 2
Potential adverse effects with commonly used urate-lowering therapies

Drug	Important side effects	Contraindications
Allopurinol	Rash	Hypersensitivity to allopurinol
	Abnormal liver function tests	HLA-B*5801 carrier
	Allopurinol hypersensitivity syndrome/DRESS/SCAR	Azathioprine use
Febuxostat	Abnormal liver function tests	Use with caution in heart failure and ischaemic heart disease
	Hypersensitivity	Azathioprine use
Probenecid	Urolithiasis	Urolithiasis
	Blood dyscrasias	

Stamp et al. Seminars Arthitis Rheum 2017

Traitements hypouricémiants : effets secondaires

	Allopurinol	Febuxostat	Probenecid	Benzbromarone	Pegloticase
Mechanism of action	Xanthine oxidase inhibitor: prevents urate production	Xanthine oxidase inhibitor: prevents urate production	Increases renal urate excretion	Increases renal urate excretion	Recombinant uricase: breaks down urate to water-soluble allantoin
Metabolism and excretion	Metabolised by aldehyde oxidase to oxypurinol, which is excreted predominantly by the kidneys	Hepatic: conjugation by uridine diphosphate-glucuronosyltransferase enzymes and oxidation to active metabolites by CYP1A2, CYP2C8, and CYP2C9; excreted via the kidneys	Oxidation of alkyl side chains and glucuronide conjugation; excreted via kidneys	Hepatic metabolism by CYP2C9 and CYP1A2; mainly excreted in bile and faeces, 6% excreted via kidneys	Renal excretion
Contraindications	Hypersensitivity to allopurinol	Use with caution in heart failure and ischaemic heart disease	Blood dyscrasias, uric acid kidney stones	Liver disease, porphyria; use with caution in patients with excess alcohol intake and history of kidney stones	Glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis and methaemoglobinaemia); repeated infusion contraindicated if serum urate response is lost
Clinically important drug interactions	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression; warfarin (increased anticoagulant effects); diuretics (possible increased risk of allopurinol hypersensitivity syndrome)	Azathioprine increases 6-mercaptopurine concentrations, resulting in myelosuppression	Aspirin; methotrexate (can increase methotrexate's toxic effects	Warfarin (increased anticoagulant effects); sulphonylureas—checkblood glucose Phenytoin Fluconazole—avoid combination Rifampicin—avoid combination	Other urate-lowering therapies can mask lack of response to pegloticase and thereby increase risk of infusion reaction; other PEGylated drugs
Dosing	50–900 mg daily (maximum of 800 mg approved by US FDA), which should be titrated to achieve target serum urate*	40–120 mg daily (maximum of 80 mg approved by US FDA), which should be titrated to achieve target serum urate	500–1000 mg twice a day	50–200 mg daily	8 mg intravenous infusion every 2 weeks
Important side-effects	Gout flares when initiating treatment, rash, allopurinol hypersensitivity syndrome	Gout flares when initiating treatment, abnormal liver function tests	Gout flares when initiating treatment, kidney uric acid stones	Gout flares when initiating treatment, hepatotoxic effects, kidney uric acid stones	Gout flares when initiating treatment, infusion reactions, immunogenic effects
Monitoring	Serum urate, renal and liver function	Serum urate, renal and liver function	Serum urate, renal function	Serum urate, liver function	Serum urate (loss of serum urate response precedes infusion reactions)
Special considerations	Dose escalation above renal based doses and above 300 mg daily to achieve target serum urate can be done with appropriate monitoring of renal and liver function and education about rash	Hypersensitivity might occur rarely in patients with prior allopurinol hypersensitivity	Advise about high fluid intake and consider urine alkalinisation to reduce risk of kidney stones	Advise about high fluid intake and consider urine alkalinisation to reduce risk of kidney stones	Should not be used with other urate-lowering therapies
Anti-inflammatory prophylaxis when commencing drug	Yes	Yes	Yes	Yes	Yes

CYP=cytochrome P450. PEG=polyethylene glycol. FDA=Food and Drug Administration. *Starting dose based on estimated glomerular filtration rate (eGFR): <30 mL/min per 1·73 m²—1·5 mg/mL eGFR; 30–60 mL/min per 1·73 m²—50 mg daily; >60 mL/min per 1·73 m²—100 mg daily. Dose escalation monthly until target serum urate is achieved. Increase in increments of 100 mg monthly if estimated glomerular filtration rate >60 mL/min per 1·73 m² and 50 mg monthly if <60 mL/min per 1·73 m².

Table 3: Prescribing and monitoring of urate-lowering drugs

Dalbeth et al. Lancet 2015

Hôpitaux Universitaires Genève

Traitements hypouricémiants : effets secondaires

	Allopurinol	Febuxostat	Probenecid	Benzbromarone	Pegloticase
Mechanism of action	Xanthine oxidase inhibitor: prevents urate production	Xanthine oxidase inhibitor: prevents urate production	Increases renal urate excretion	Increases renal urate excretion	Recombinant uricase: breaks down urate to water-soluble allantoin
Metabolism and excretion	Metabolised by aldehyde oxidase to oxypurinol, which is excreted predominantly by the kidneys	Hepatic: conjugation by uridine diphosphate-glucuronosyltransferase enzymes and oxidation to active metabolites by CYP1A2, CYP2C8, and CYP2C9; excreted via the kidneys	Oxidation of alkyl side chains and glucuronide conjugation; excreted via kidneys	Hepatic metabolism by CYP2C9 and CYP1A2; mainly excreted in bile and faeces, 6% excreted via kidneys	Renal excretion
Dosing	50–900 mg daily (maximum of 800 mg approved by US FDA), which should be titrated to achieve target serum urate*	40–120 mg daily (maximum of 80 mg approved by US FDA), which should be titrated to achieve target serum urate			
Important side-effects	Gout flares when initiating treatment, rash, allopurinol hypersensitivity syndrome	Gout flares when initiating treatment, abnormal liver function tests			
Monitoring	Serum urate, renal and liver function	Serum urate, renal and liver function			
Special considerations	Dose escalation above renal based doses and above 300 mg daily to achieve target serum urate can be done with appropriate monitoring of renal and liver function and education about rash	Hypersensitivity might occur rarely in patients with prior allopurinol hypersensitivity			
Anti-inflammatory prophylaxis when commencing drug	Yes	Yes			

uric acid | Liver disease, porphyria; use with caution in patients with excess alcohol intake and history of kidney stones | Glucose-6-phosphate dehydrogenase deficiency (risk of haemolysis and methaemoglobinaemia); repeated infusion contraindicated if serum urate response is lost

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vice a day | 50–200 mg daily | 8 mg intravenous infusion every 2 weeks

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al | Serum urate, liver function | Serum urate (loss of serum urate response precedes infusion reactions)

h fluid der urine reduce risk | Advise about high fluid intake and consider urine alkalinisation to reduce risk of kidney stones | Should not be used with other urate-lowering therapies

Yes | Yes

ed glomerular filtration rate (eGFR): <30 mL/min per 1·73 m²—1·5 mg/mL. eGFR; erum urate is achieved. Increase in increments of 100 mg monthly if estimated glomerular

Dalbeth et al. Lancet 2015

Hôpitaux Universitaires Genève

Allopurinol et syndrome de Lyell

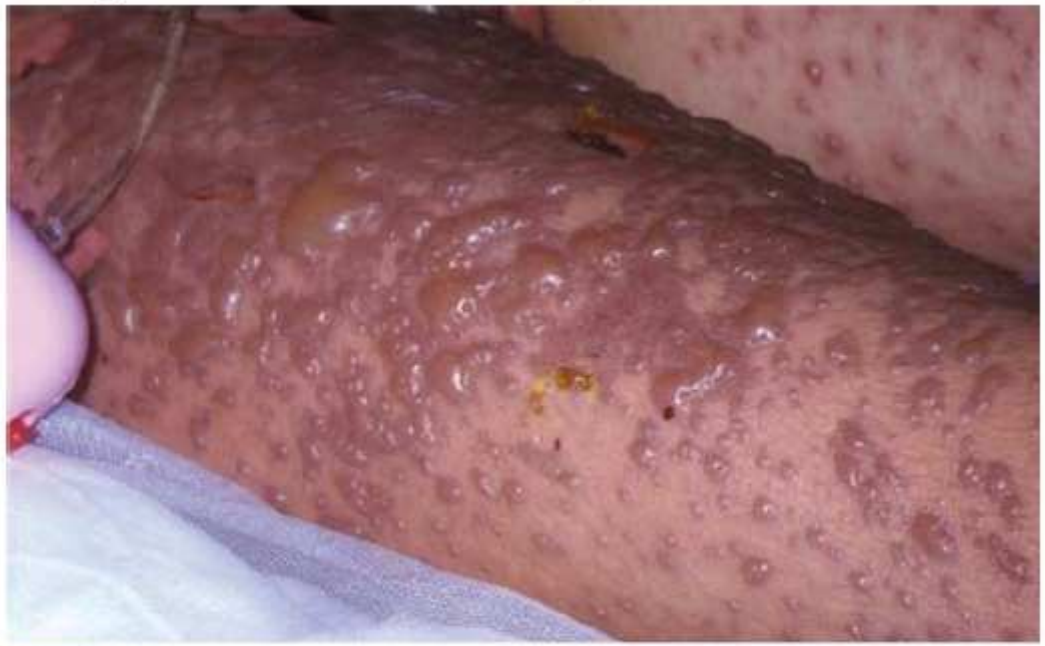

Figure 1 **Aspect précoce de nécrolyse épidermique.** Bulles à toit nécrotique (couleur ardoisée).

Roujeau et al. Rev Prat 2007

Débuter l'allopurinol à 1.5 mg/mlGFR réduit le risque d'hypersensibilité à l'allopurinol

Stamp et al. Arthitis Rheum 2012

Traitements hypouricémiants : effets secondaires

Risk of Febuxostat-Associated Myopathy in Patients with CKD

Chung-te Liu,[*†] *Chun-You Chen,*[‡] *Chien-Yi Hsu,*[†§‖¶] *Po-Hsun Huang,*[§‖**] *Feng-Yen Lin,*[†¶] *Jaw-Wen Chen,*[‖**††‡‡] *and Shing-Jong Lin*[§‖**††§§]

Table 1. Demographic characteristics and time-averaged laboratory data of febuxostat users with or without myopathy

Characteristics	Total	Nonmyopathy	Myopathy	*P* Value
No.	1332	1291	41	—
Age, yr (mean ± SD)	71.5±14.8	71.5±14.8	71.5±15.4	0.99
Men, *n* (%)	925 (69.4)	894 (69.3)	31 (75.6)	0.38
CKD, *n* (%)	1222 (91.7)	1181 (91.5)	41 (100)	0.04[a]
ESRD, *n* (%)	99 (7.4)	92 (7.1)	7 (17.0)	0.03[a]
DM, *n* (%)	626 (47.0)	604 (46.8)	22 (53.7)	0.39
CAD, *n* (%)	645 (48.4)	626 (48.5)	19 (46.3)	0.79
Hypertension, *n* (%)	1208 (90.7)	1168 (90.5)	40 (97.6)	0.17[a]
Statin or fibrate use, *n* (%)	685 (51.4)	661 (51.2)	24 (58.5)	0.35
Serum creatinine,[b] mg/dl	1.7 (1.4, 2.5)	1.7 (1.4, 2.5)	2.6 (1.7, 3.4)	0.01
eGFR,[b] ml/min per 1.73 m^2	20.8 (9.0, 35.4)	21.3 (9.4, 35.9)	7.3 (2.5, 21.9)	<0.001
Serum uric acid, mg/dl (mean ± SD)	8.2±2.1	8.2±2.1	8.5±2.1	0.33
T. chol, mg/dl (mean ± SD)	172.4±44.7	172.0±44.4	179.3±50.5	0.45
Duration,[b] d	224 (86, 442)	223 (84, 440)	303 (166, 515)	0.03
Daily dose (DDD) (mean ± SD)	0.8±0.6	0.8±0.6	0.8±0.3	0.50
CK tests[b]	0 (0, 1)	0 (0, 0)	3 (2, 5)	<0.001
Creatinine tests[b]	6 (3, 9)	5 (3, 9)	11 (7, 14)	<0.001

eGFR was calculated by the equation proposed by the Chronic Kidney Disease Epidemiology Collaboration in 2009. —, not applicable; DM, diabetes mellitus; CAD, coronary artery disease; T. chol, serum total cholesterol; DDD, defined daily dose suggested by the World Health Organization Collaborating Center for Drug Statistics Methodology.
[a]Significance tested by Fisher exact test.
[b]Expressed as median (25th, 75th percentiles).

CJASN (in press)

Hôpitaux Universitaires Genève

En conclusion : faut-il traiter l'hyperuricémie assymptomatique ?

- **Recommandations de bonne pratique:**

Patients avec hyperuricémie assymptomatique sans IRC:

Non

Patients avec hyperuricémie assymptomatique avec IRC:

Peut-être mais:

-débuter avec petites doses , augmentation très progressive doses ou maintien à 100 mg/jour ?

-éducation du patient

-monitoring régulier enzymes hépatiques, fonction rénale

Et n'oublions pas le régime…

Clin Rheumatol
DOI 10.1007/s10067-017-3613-x

BRIEF REPORT

DASH diet and change in serum uric acid over time

Olive Tang[1,2] · Edgar R. Miller III[1,2,3] · Allan C. Gelber[1,2,3] · Hyon K. Choi[4] · Lawrence J. Appel[1,2,3] · Stephen P. Juraschek[1,2,3]

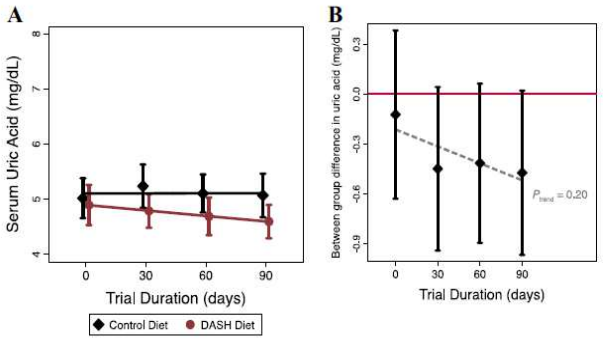

Fig. 1 Effect of DASH diet on uric acid. a Mean serum uric acid levels at baseline, 30, 60, and 90 days according to assignment to the DASH diet (*red*) or control diet (*black*). b Differences in mean serum uric acid levels at baseline, 30, 60, and 90 days. *Vertical lines* represent 95% confidence intervals. The *P* value reflects linear regression of differences (control minus DASH) over visit at baseline, 30, 60, or 90 days modeled as a categorical variable (Color figure online)

Baisse moyenne de 30 µmol/L de l'uricémie après un mois!

Et de 48 µmol/L à un mois et de 60 µmol/L à 3 mois chez patients avec uricémie de base > 360