Asymptomatic hyperuricaemia: to treat or not to treat?

Lazaros I. Sakkas, MD, DM, PhD, FRCP
Emeritus Professor of Medicine and Rheumatology,
University of Thessaly, Larissa

Asymptomatic hyperurecaemia(aHU)- the size of the problem

- 10-20% of adult individuals

Mikuls TR Ann Rheum Dis 2005;64:267

Zhu Y Arthritis Rheum 2011;63:3136

Kapenanovic MC Arthritis Res Ther 2018;20:190

Kapetanovic et al. Arthritis Research & Therapy (2018) 20:190
https://doi.org/10.1186/s13075-018-1697-6

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

The risk of clinically diagnosed gout by serum urate levels: results from 30 years follow-up of the Malmö Preventive Project cohort in southern Sweden

Meliha C. Kapetanovic[1*], Peter Nilsson[2,3], Carl Turesson[4], Martin Englund[5], Nicola Dalbeth[6] and Lennart Jacobsson[7]

33,335 participants, Follow up (mean): 28.2 years
At baseline HU was correlated with
BMI,
lower eGFR,
Hypertension,
DM,
CVD,
kidney stones,
ESR,
alcohol(men)

J Clin Hypertens (Greenwich). 2016 Jan;18(1):53-9. doi: 10.1111/jch.12627. Epub 2015 Jul 25.

Association Between Serum Uric Acid Levels/Hyperuricemia and Hypertension Among 85,286 Japanese Workers.

Yokokawa H[1], Fukuda H[1], Suzuki A[1], Fujibayashi K[1], Naito T[1], Uehara Y[1], Nakayama A[2], Matsuo H[2], Sanada H[3,4], Jose PA[5], Miwa Y[6], Hisaoka T[1], Isonuma H[1].

Arthritis Rheum. 2009 July 15; 61(7): 885–892. doi:10.1002/art.24612.

Hyperuricemia and Risk of Stroke: A Systematic Review and Meta-analysis

Seo Young Kim, MD[1,2], James P Guevara, MD, MPH[2,3], Kyoung Mi Kim, MD[4], Hyon K Choi, MD, DrPH[5], Daniel F. Heitjan, PhD[2,6], and Daniel A Albert, MD[7]

Elevated SUA is an independent risk factor for stroke (RR:1.47[1.19-1.76])
and stroke mortality (RR:1.26[1.12-1.39])

Eur J Clin Nutr. 2019 Feb 20. doi: 10.1038/s41430-019-0405-1. [Epub ahead of print]

Asymptomatic hyperuricemia and incident stroke in elderly Chinese patients without comorbidities.

Tu W[1], Wu J[2], Jian G[2], Lori J[3], Tang Y[4], Cheng H[4], Wu X[5], Wang N[6].

Asymptomatic hyperuricemia carried
a significant risk of stroke events

Journal of Cardiovascular Translational Research
https://doi.org/10.1007/s12265-018-9843-8

ORIGINAL ARTICLE

Serum Uric Acid Is Independently Associated with Coronary Calcification in an Asymptomatic Population

Loretta Zsuzsa Kiss[1] · Zsolt Bagyura[1] · Csaba Csobay-Novák[1] · Árpád Lux[1] · Lívia Polgár[1] · Ádám Jermendy[1] · Pál Soós[1] · Zsolt Szelid[1] · Pál Maurovich-Horvat[1,2] · Dávid Becker[1] · Béla Merkely[1]

Arthritis Care Res (Hoboken). 2010 February ; 62(2): 170–180. doi:10.1002/acr.20065.

Hyperuricemia and Coronary Heart Disease: A Systematic Review and Meta-Analysis

Seo Young Kim, MD, MSCE[1,2], James P. Guevara, MD, MPH[3,4], Kyoung Mi Kim, MD[5], Hyon K. Choi, MD, DrPH[6], Daniel F. Heitjan, PhD[3,7], and Daniel A. Albert, MD[8]

Elevated SUA increased CHD mortality in women(RR:1.67[1.30-2.04])

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2014) **16**, 15–24
doi:10.1093/eurjhf/hft132

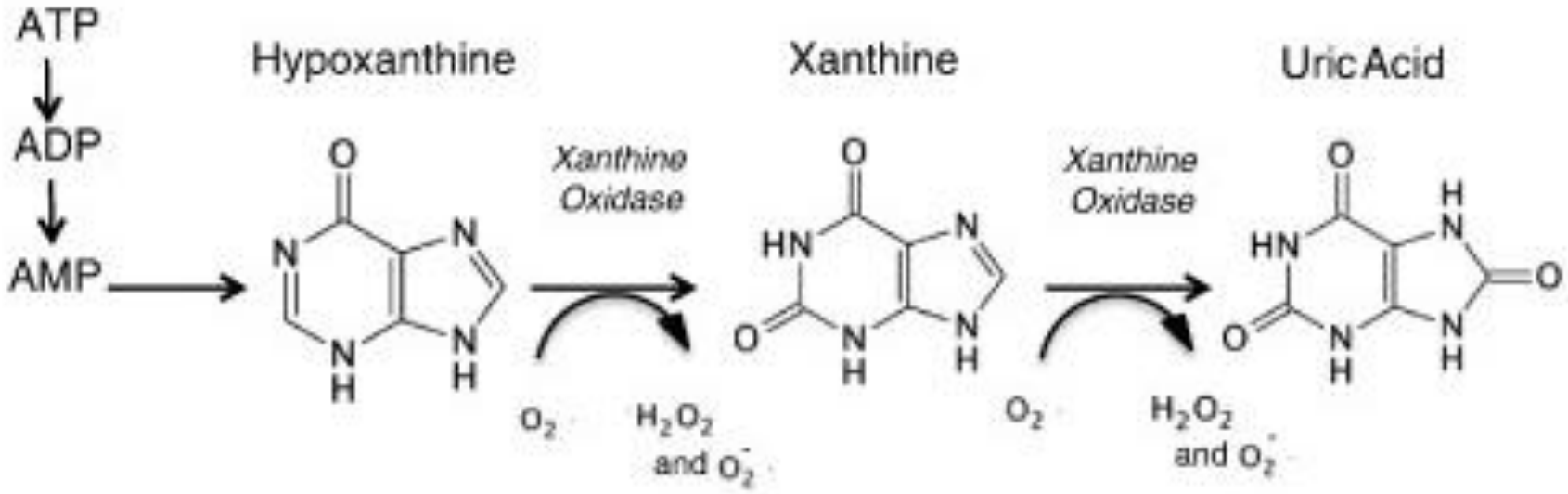
Uric acid and risk of heart failure: a systematic review and meta-analysis

He Huang[1], Baotao Huang[1], Yulin Li[3], Yan Huang[2], Jing Li[2*], Hongmei Yao[1], Xianchao Jing[1], Jianrong Chen[2], and Ji Wang[2]

Elevated SUA is an independent risk factor for CVD and heart failure

Elevated sUA: cause or biomarker of disease?

During UA generation reactive oxygen species are produced



Okafor ON Pharmacol Ther 2017;172:139

Proc. Natl. Acad. Sci. USA
Vol. 78, No. 11, pp. 6858–6862, November 1981
Biochemistry

Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis

(lipid peroxidation/ascorbic acid/primate evolution/erythrocyte aging)

BRUCE N. AMES*, RICHARD CATHCART*, ELIZABETH SCHWIERS*, AND PAUL HOCHSTEIN†

Table 2. Effect of urate and ascorbate on *t*-butylhydroperoxide-induced hemolysis of human erythrocytes

Additions	% hemolysis		
	4 hr	7 hr	20 hr
None	0	0	3 ± 1
t-Butylhydroperoxide at 200 μM	5 ± 1	14 ± 1	100 ± 2
+ Urate at 10 μM	0	4 ± 1	17 ± 2
50 μM	0	0	5 ± 1
100 μM	0	0	6 ± 1
+ Ascorbate at 10 μM	0	2 ± 1	9 ± 2
50 μM	0	0	5 ± 1
100 μM	0	0	4 ± 1

Serum UA is a strong antioxidant

Biochem. J. (1986) 235, 747–754 (Printed in Great Britain)

Uric acid–iron ion complexes

A new aspect of the antioxidant functions of uric acid

Kelvin J. A. DAVIES,*†§ Alex SEVANIAN,*‡ Samar F. MUAKKASSAH-KELLY* and Paul HOCHSTEIN*†
*Institute for Toxicology, †Department of Biochemistry and ‡Department of Pathology, University of Southern California, 1985 Zonal Avenue, HSC-PSC 614-616, Los Angeles, CA 90033, U.S.A.

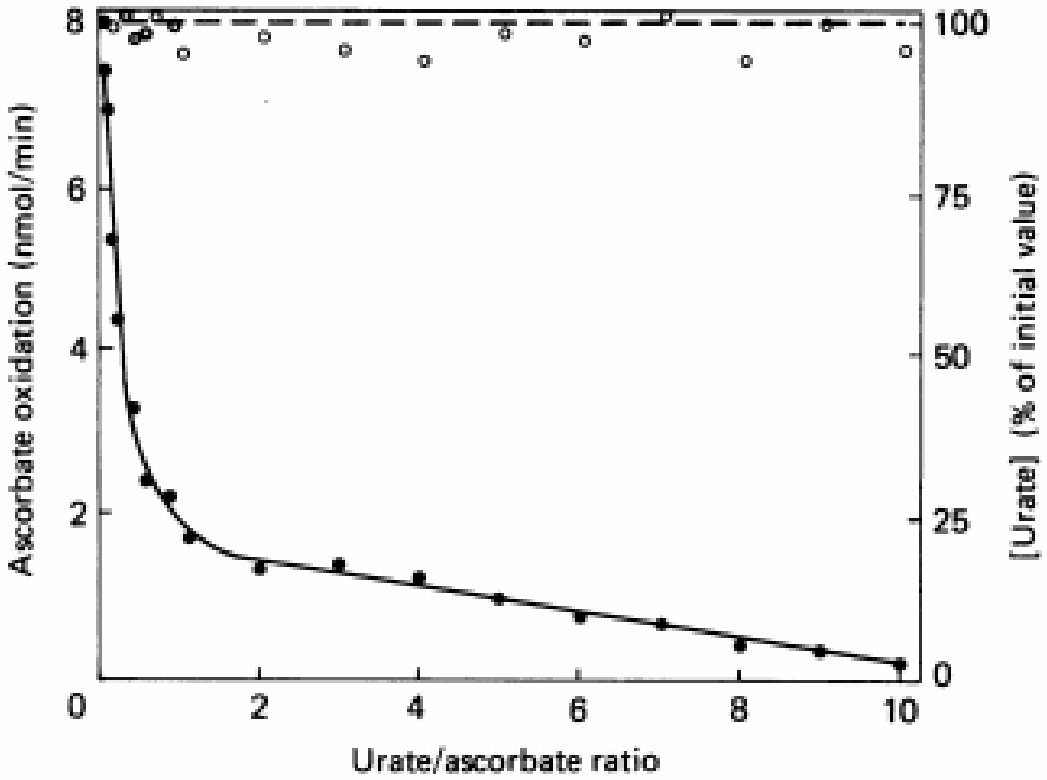


Fig. 2. Inhibition of ascorbate oxidation by urate

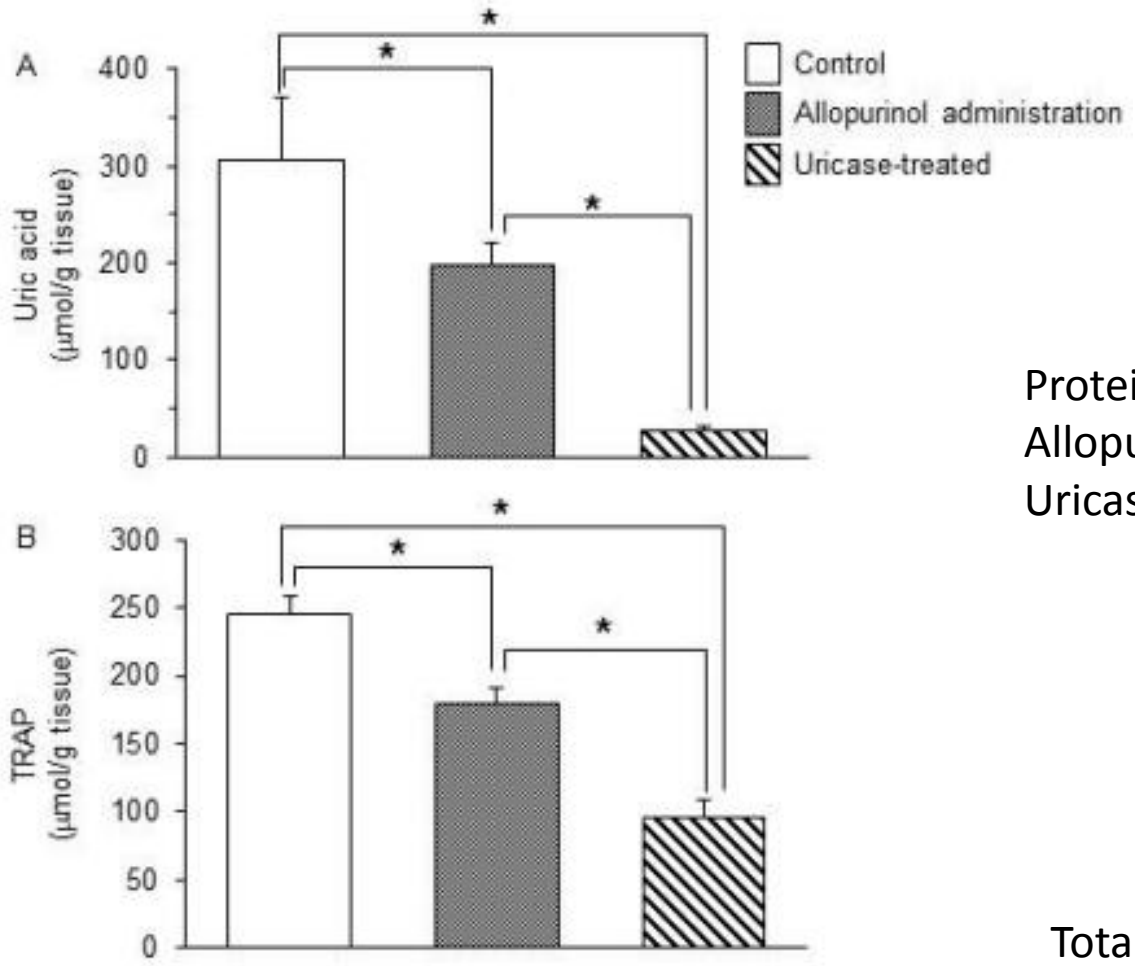
Initial rates of oxidation of 100 μM-ascorbate (●) measured by decrease in A_{265} in the presence of 10 μM-$FeCl_3$ ± urate, and percentages of initial urate concentrations (5.0 μM–1.0 mM) remaining (○) after 1 min incubations with 100 μM-ascorbate + 10 μM-$FeCl_3$. Experi-

Physiol. Res. 66: 1001-1007, 2017

Uric Acid Contributes Greatly to Hepatic Antioxidant Capacity Besides Protein

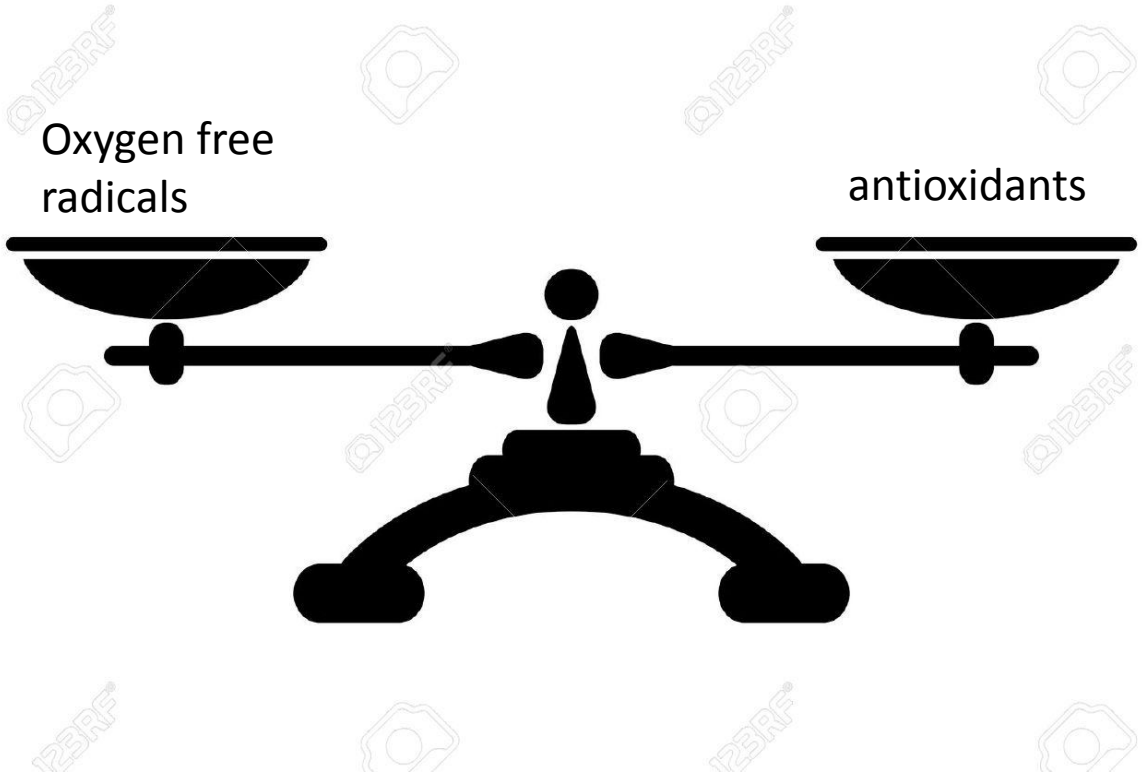
T. MIKAMI[1], M. SORIMACHI[2]

UA is a strong antioxidant in tissues



Protein-free hepatic cytosol
Allopurinol-treated mice
Uricase in protein-free hepatic cytosol of control mice

Total-radical trapping antioxidant parameter(TRAP)



Oxygen free radicals >> antioxidants: oxidative stress

Observational Study

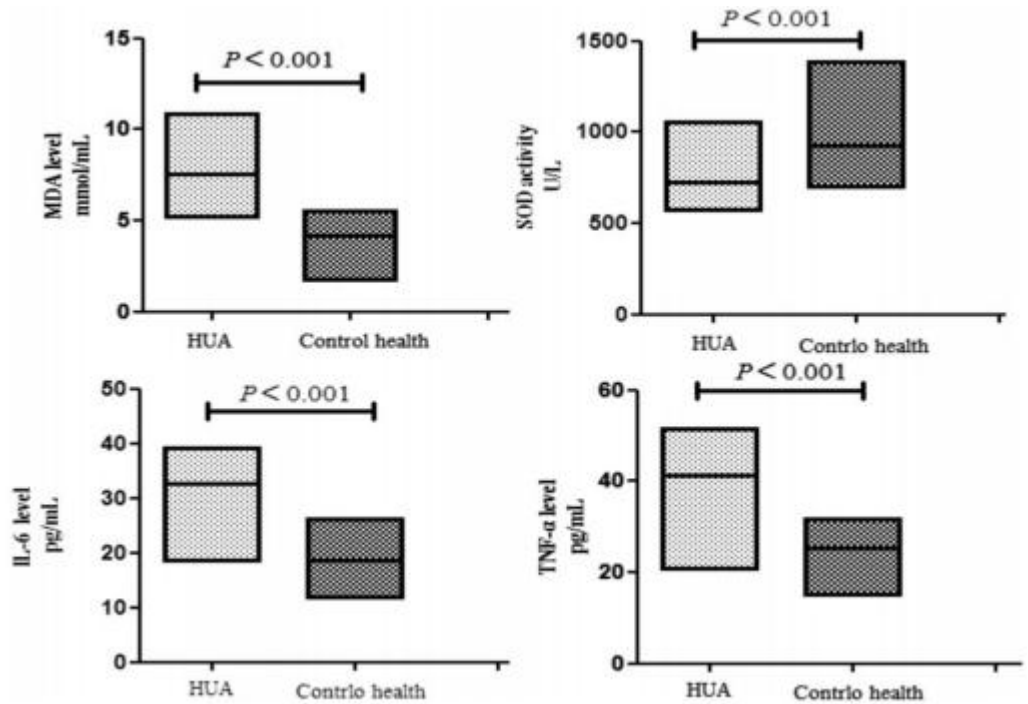
Medicine

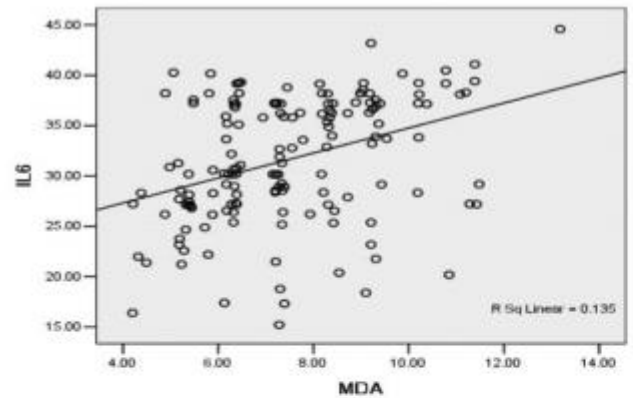
OPEN

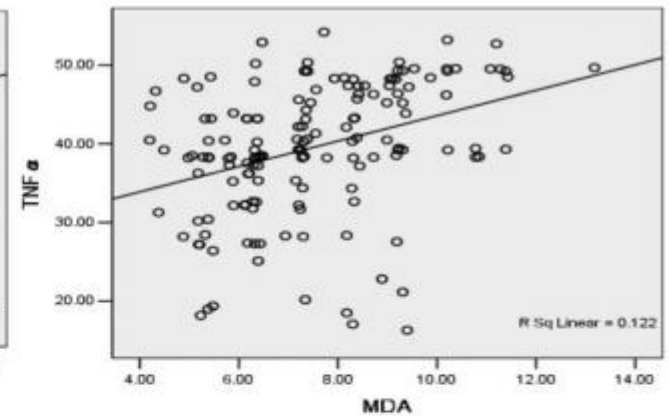
Relationship between oxidative stress and inflammation in hyperuricemia

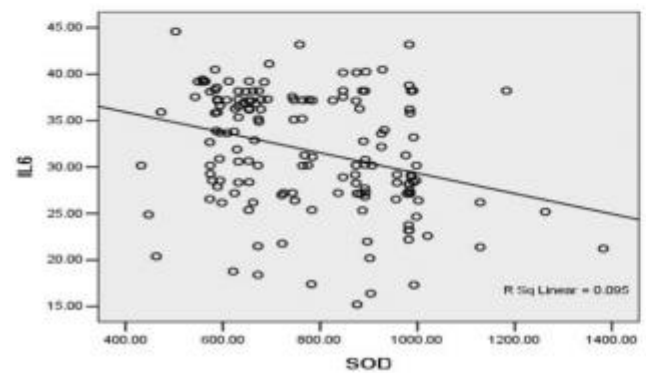
Analysis based on asymptomatic young patients with primary hyperuricemia

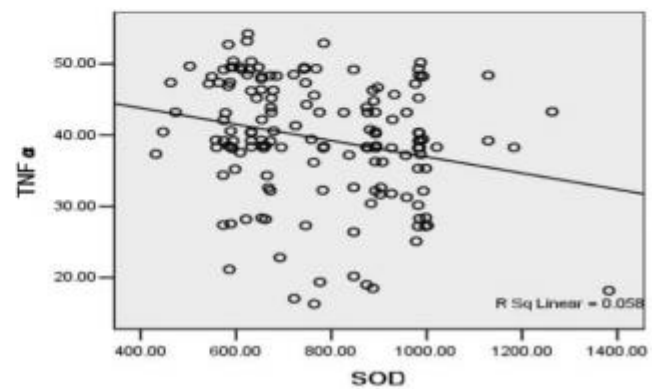
You Zhou, MS, Mingcai Zhao, PhD*, Zheyan Pu, MD, Guoqiang Xu, MD, Xiangkun Li, MD





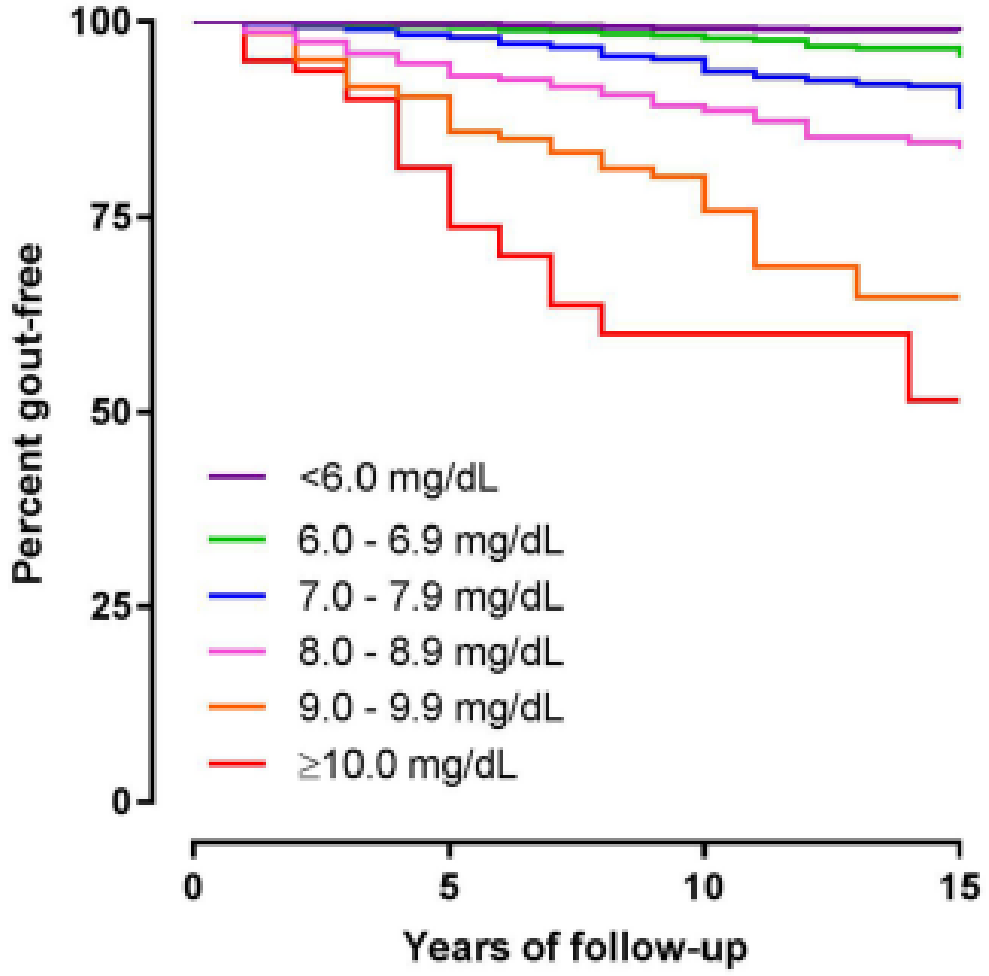






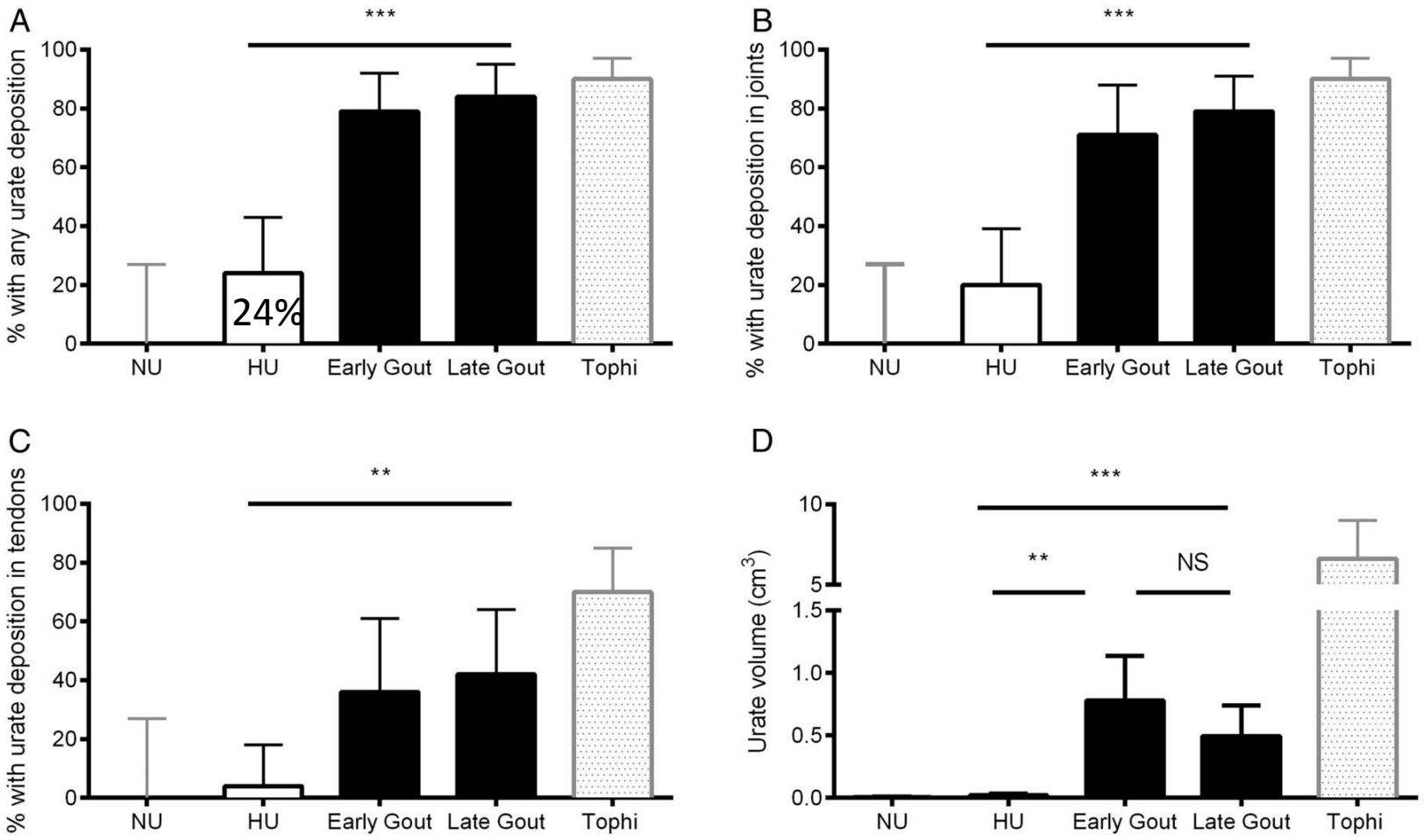
MDA:malondialdehyde
SOD:superoxide dismutase

Only a small percentage of HU pts will develop gout after 15 years

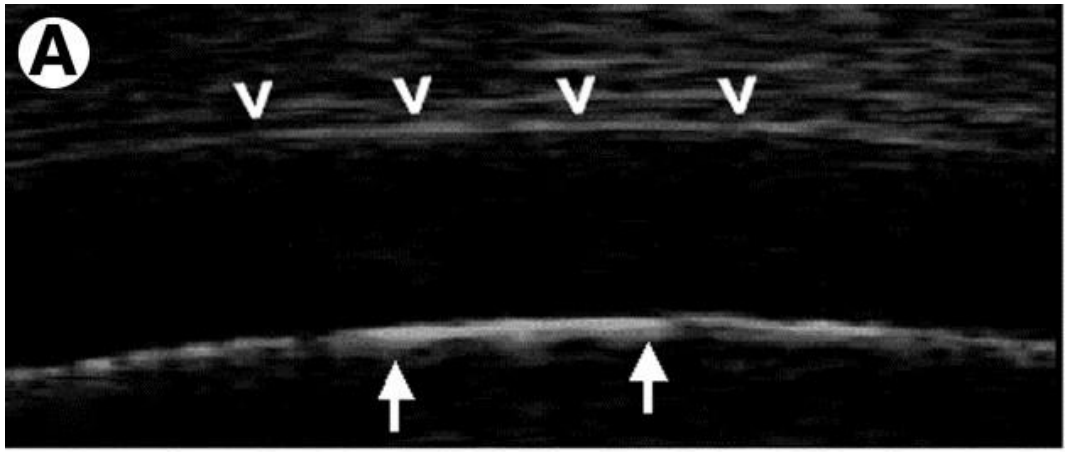


Dalbeth N Ann Rheum Dis 2018;77:1048

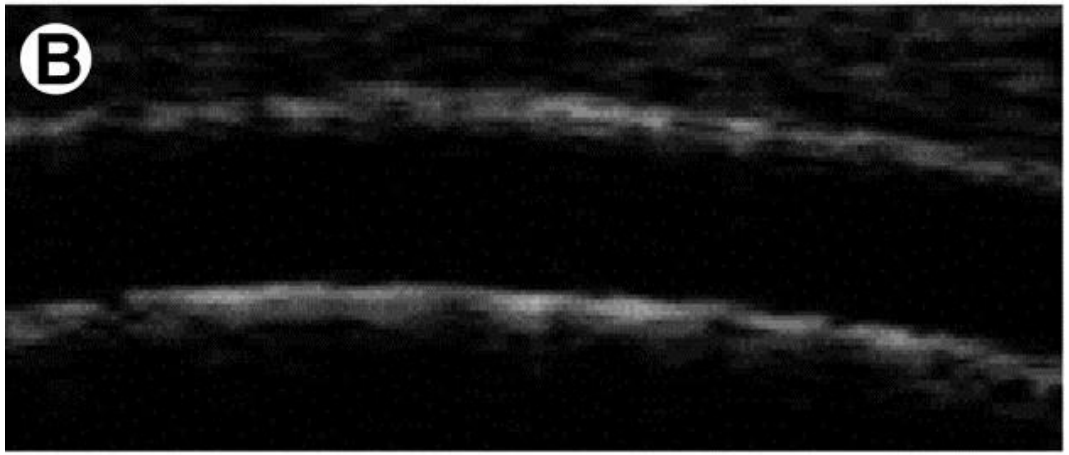
Asymptomatic HU: Urate deposition



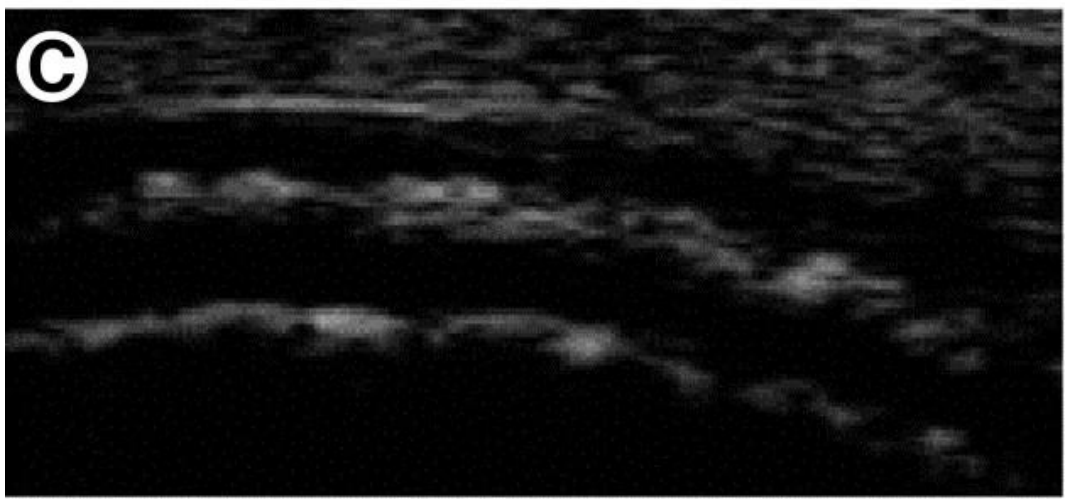
Dalbeth N, Ann Rheum Dis 2015;74:908



Normal hyaline cartilage



MSU deposition on superficial surface of cartilage



CPPD within cartilage

Grassi W, Sem AR 2006;36:197

Dual energy CT in 45 patients with asymptomatic HU
sUA:6.5-14.4 mg/dL
MSU deposits:15%

Table 1 Association between patient characteristics and presence or absence of MSU crystal deposits on DECT scans among patients with asymptomatic hyperuricemia (n=46)

Patient characteristics	Mean±SD or %	Univariable OR (95% CI)	sUA-adjusted OR (95% CI)
sUA, mg/dL	7.8±1.0	1.36 (0.63 to 2.95)	–
Age, years	62±8	1.20 (1.03 to 1.39)	1.21 (1.03 to 1.41)
Male sex	41%	1.08 (0.21 to 5.49)	1.06 (0.21 to 5.47)
Body mass index, kg/m^2	36.4±6.3	0.97 (0.85 to 1.11)	0.94 (0.81 to 1.10)
Type 2 diabetes	54%	0.97 (0.19 to 4.93)	0.87 (0.16 to 4.62)
Serum creatinine, mg/dL	1.04±0.3	0.92 (0.08 to 11.19)	0.62 (0.05 to 8.53)
hs-CRP, mg/L	8.7±14.7	1.00 (0.94 to 1.06)	1.00 (0.94 to 1.06)

DECT, dual-energy CT; hs-CRP, high-sensitivity C reactive protein; MSU, monosodium urate; sUA, serum uric acid.

Wang P RMD Open 2018;4:e000593

Arthritis Rheumatol. 2018 Nov;70(11):1847-1852. doi: 10.1002/art.40572. Epub 2018 Aug 27.

Brief Report: Monosodium Urate Monohydrate Crystal Deposits Are Common in Asymptomatic Sons of Patients With Gout: The Sons of Gout Study.

Abhishek A[1], Courtney P[2], Jenkins W[1], Sandoval-Plata G[1], Jones AC[2], Zhang W[1], Doherty M[1].

131 sons(sUA ≥6 mg/dL in 64.1%)
1st MTP MSU deposits: 29.8%

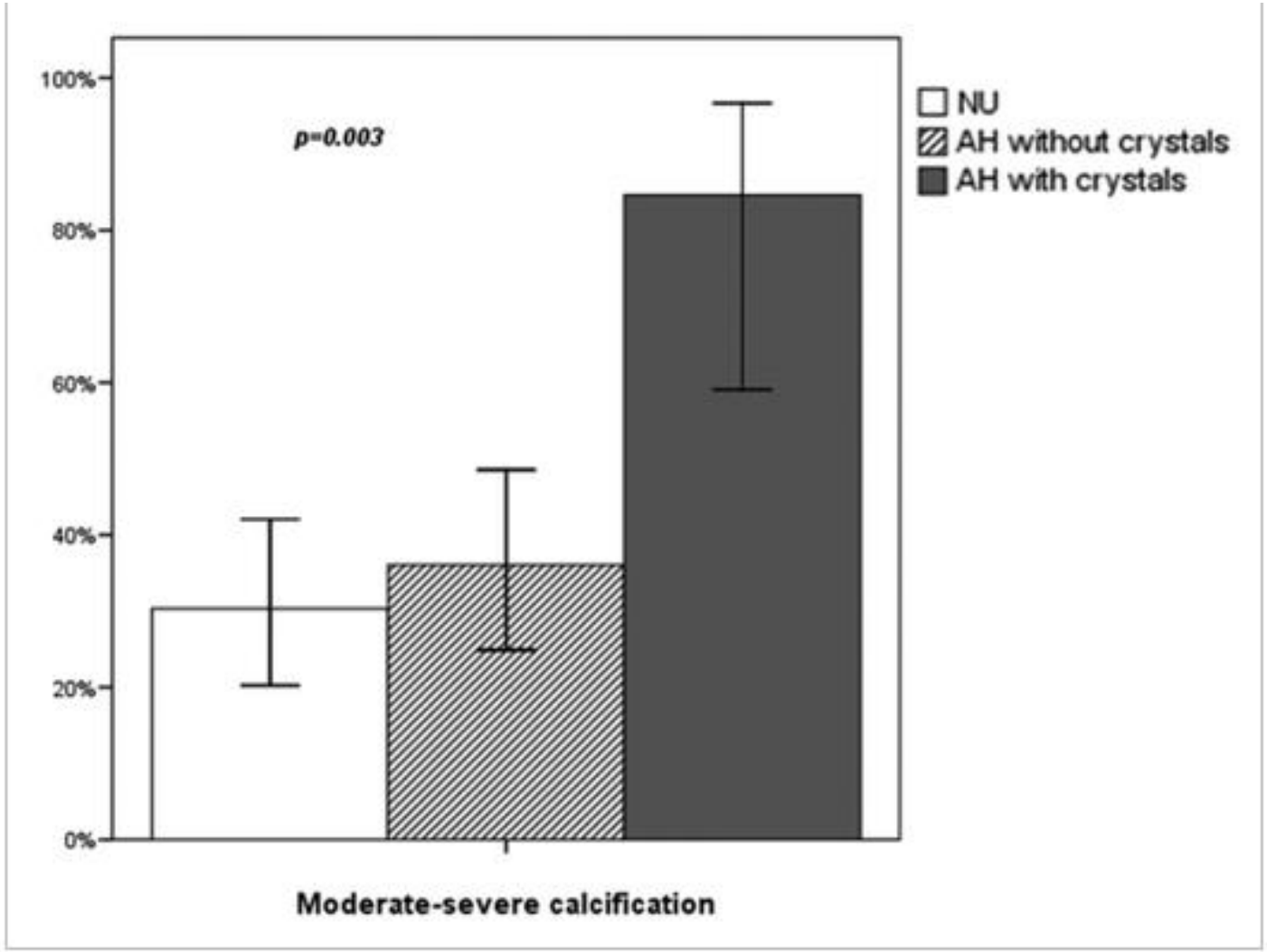
No MSU deposits in pts with sUA <5 mg/dL

MSU deposits correlated with joint effusion:
-RRadj:9.4 (95%CI 3.6-24.6)

Arthritis Rheumatol. 2016 Jun;68(6):1531-9. doi: 10.1002/art.39581.

Silent Monosodium Urate Crystal Deposits Are Associated With Severe Coronary Calcification in Asymptomatic Hyperuricemia: An Exploratory Study.

Andrés M[1], Quintanilla MA[2], Sivera F[2], Sánchez-Payá J[3], Pascual E[4], Vela P[4], Ruiz-Nodar JM[3].



thebmj

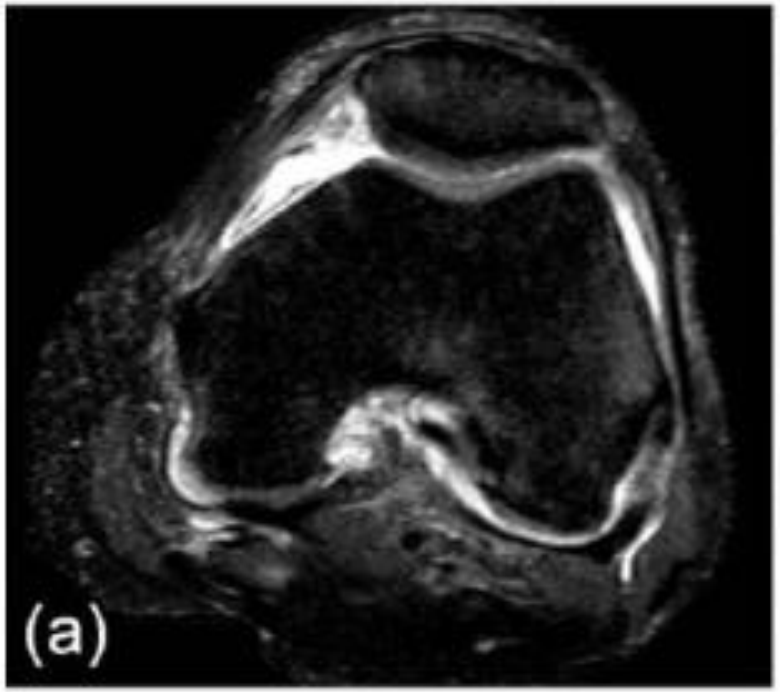
BMJ 2017;357:j2376 doi: 10.1136/bmj.j2376 (Published 7 June 2017)

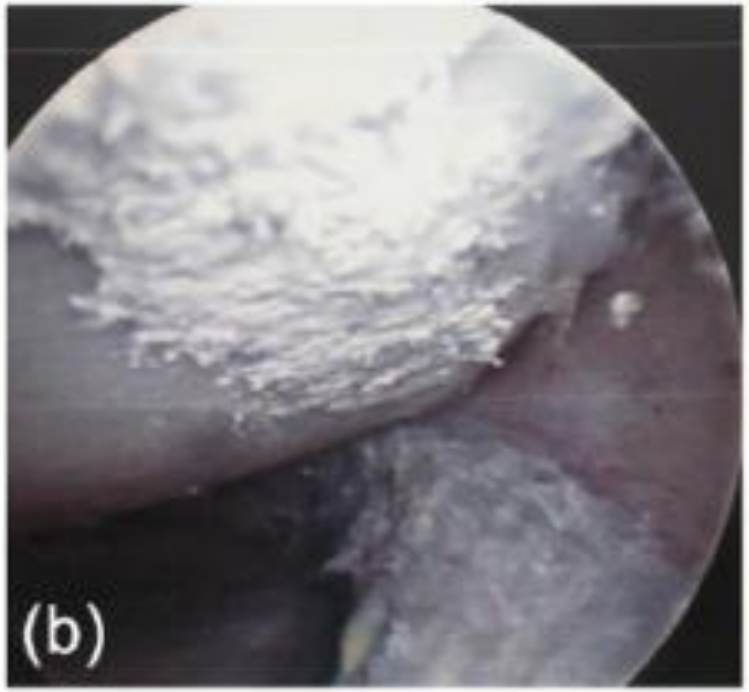
RESEARCH

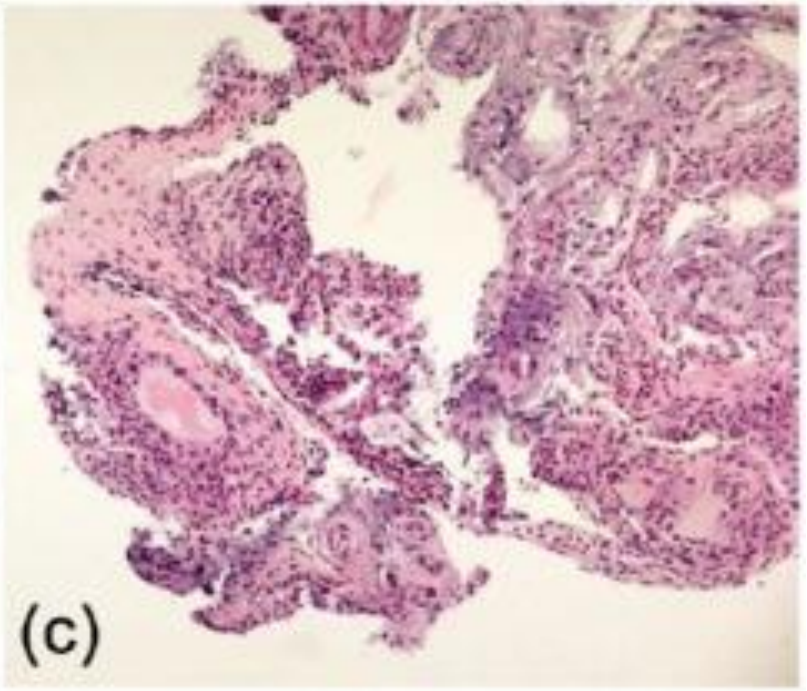
Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies

Xue Li *PhD student*[1], Xiangrui Meng *PhD student*[1], Maria Timofeeva *statistical geneticist*[2], Ioanna Tzoulaki *senior lecturer*[3], Konstantinos K Tsilidis *assistant professor*[3 4], John PA Ioannidis *professor*[5 6 7], Harry Campbell *professor*[1], Evropi Theodoratou *chancellor's fellow*[1 2]

Conclusion Despite a few hundred systematic reviews, meta-analyses, and Mendelian randomisation studies exploring 136 unique health outcomes, convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis.





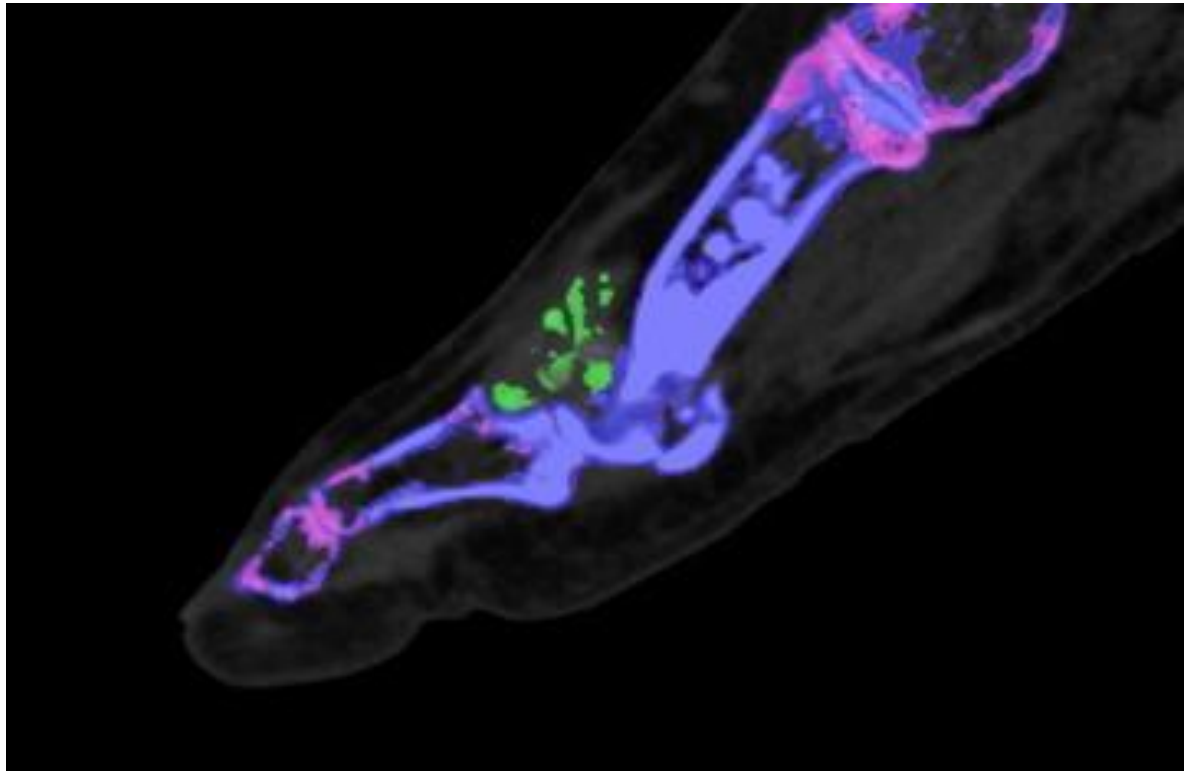


MRI: no crystals

Arthroscopy:crystals

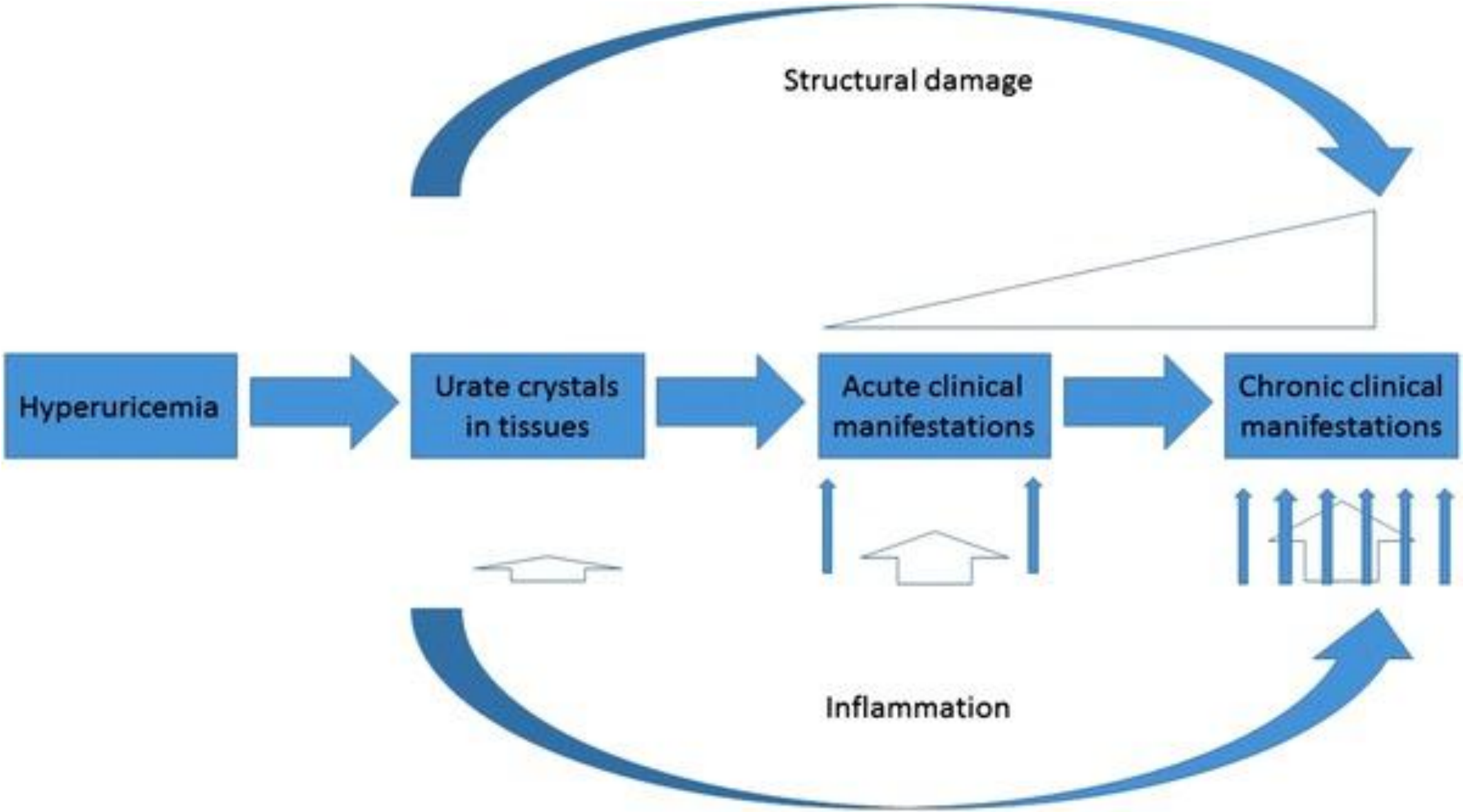
Biopsy:granulomatous inflammation

In a patient with 1st attack of gout



Patient with tophaceous gout
2-dimensonalm DECT: crystals within an erosion

Perez-Ruiz F Adv Ther 2015’;32:31



Perez-Ruiz Adv Ther 2015;32:31

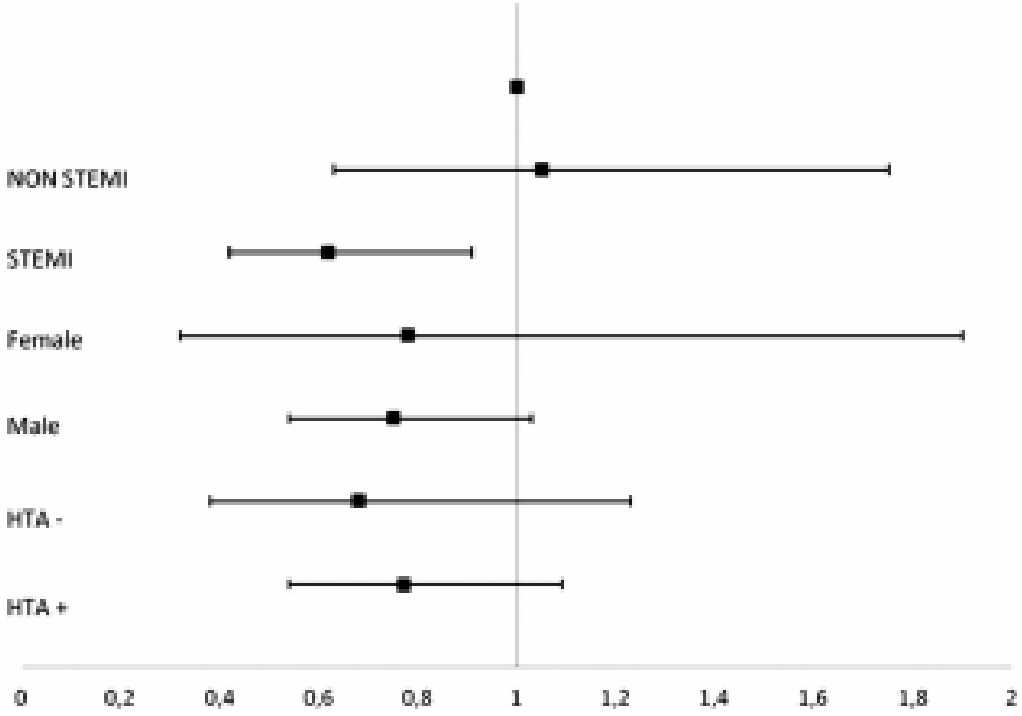
Does ULT improve outcome?

J Investig Med. 2015 Dec;63(8):924-9. doi: 10.1097/JIM.0000000000000242.

Lowering Uric Acid With Allopurinol Improves Insulin Resistance and Systemic Inflammation in Asymptomatic Hyperuricemia.

Takir M[1], Kostek O, Ozkok A, Elcioglu OC, Bakan A, Erek A, Mutlu HH, Telci O, Semerci A, Odabas AR, Afsar B, Smits G, ALanaspa M, Sharma S, Johnson RJ, Kanbay M.

Allopurinol might decrease the risk of myocardial infarction



Dalbeth N, Ann Rheum Dis 2015;74:908

Cochrane Database Syst Rev. 2017 Apr 13;4:CD008652. doi: 10.1002/14651858.CD008652.pub3.

Pharmacotherapy for hyperuricemia in hypertensive patients.

Gois PHF[1], Souza ERM[2].

AUTHORS' CONCLUSIONS: the RCT data available at present are insufficient to know whether UA-lowering therapy also lowers BP. More studies are needed.

Rheumatology (Oxford). 2017 Jul 1;56(7):1144-1153. doi: 10.1093/rheumatology/kex065.

Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis.

Zhang T[1], Pope JE[1].

CONCLUSION: RCT data do not suggest differences in CV events among ULTs in gout.
Trials had few events despite high-risk patients being enrolled and may have been too short to show CV reduction by controlling inflammatory attacks and lowering UA.

Journal of Advanced Research 8 (2017) 555–560

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journal homepage: www.elsevier.com/locate/jare

Review

Asymptomatic hyperuricemia and chronic kidney disease: Narrative review of a treatment controversial

Theodoros Eleftheriadis, Spyridon Golphinopoulos, Georgios Pissas, Ioannis Stefanidis *

Department of Nephrology, University of Thessaly, School of Medicine, Mezourlo Hill, 41110 Larissa, Greece

there may be an improvement of renal function with allopurinol. However,
-Limited No of patients.
-Insufficient information on AEs and on incidence of ESRD

Am J Kidney Dis. 2018 Dec;72(6):798-810. doi: 10.1053/j.ajkd.2018.06.028. Epub 2018 Sep 1.

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

Kimura K[1], Hosoya T[2], Uchida S[3], Inaba M[4], Makino H[5], Maruyama S[6], Ito S[7], Yamamoto T[8], Tomino Y[9], Ohno I[10], Shibagaki Y[11], Iimuro S[12], Imai N[13], Kuwabara M[14], Hayakawa H[15], Ohtsu H[16], Ohashi Y[17]; FEATHER Study Investigators.

No benefit

ULT:benefit vs harm

Withdrawal due to adverse effects(follow up 24-52 weeks)

- Allopurinol (100-300 mg/d): 77/1,000
- Febuxostat (80 mg/d): 68/1,000

Seth R, Cochrane Database Syst Rev 2014

aHU-management

- Identify cause of hyperurecemia and manage
  - Alcohol drinking
  - Drugs
- Identify comorbidities and manage
  - Hypertension
  - CV risk score
  - BMI
  - Abdominal circumference
- U/S for MSU deposits in joints, kidneys, tendons
- Monitor sUA and renal function

Stamp L, Semin AR 2017