

IN THE NAME OF  
**GOD**

"His Name Shall Be Revered"



# *Uric acid and hypertension*

*DR.roghayeh akbari*

Associate professor of babol university of medical science

# *Uric acid and hypertension*



*story of uric acid*



*Hyperuricaemia and Evolution*



*Historical Association of Hyperuricaemia and Hypertension*



*Evidence from Epidemiological studies*



*is it Causal or representative Of two conditions*



*Biological Mechanisms for Hyperuricaemia Induced Hypertension*

# uric acid

1-uric acid is a waste product created during the normal breakdown of purines

, In humans the final compound of purines catabolism is uric acid. All other mammals possess the enzyme uricase that converts uric acid to allantoin that is easily eliminated through urine

2-naturally occurring substances



# STORY OF URIC ACID

uric acid was first isolated from kidney stones in 1776 by the Swedish chemist Carl Wilhelm Scheele



*. In 1882, the Ukrainian chemist Ivan Horbaczewski first synthesized uric acid by melting urea with glycine. Solubility in water: 6 mg*



ENCYCLOPÆDIA BRITANNICA

17<sup>th</sup> International Congress of Nephrology, Dialysis, and Transplantation

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Tabriz, Iran 19-22 November 2019



International Society of Nephrology



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# *Uric acid and hypertension*



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***Evidence from Epidemiological studies***



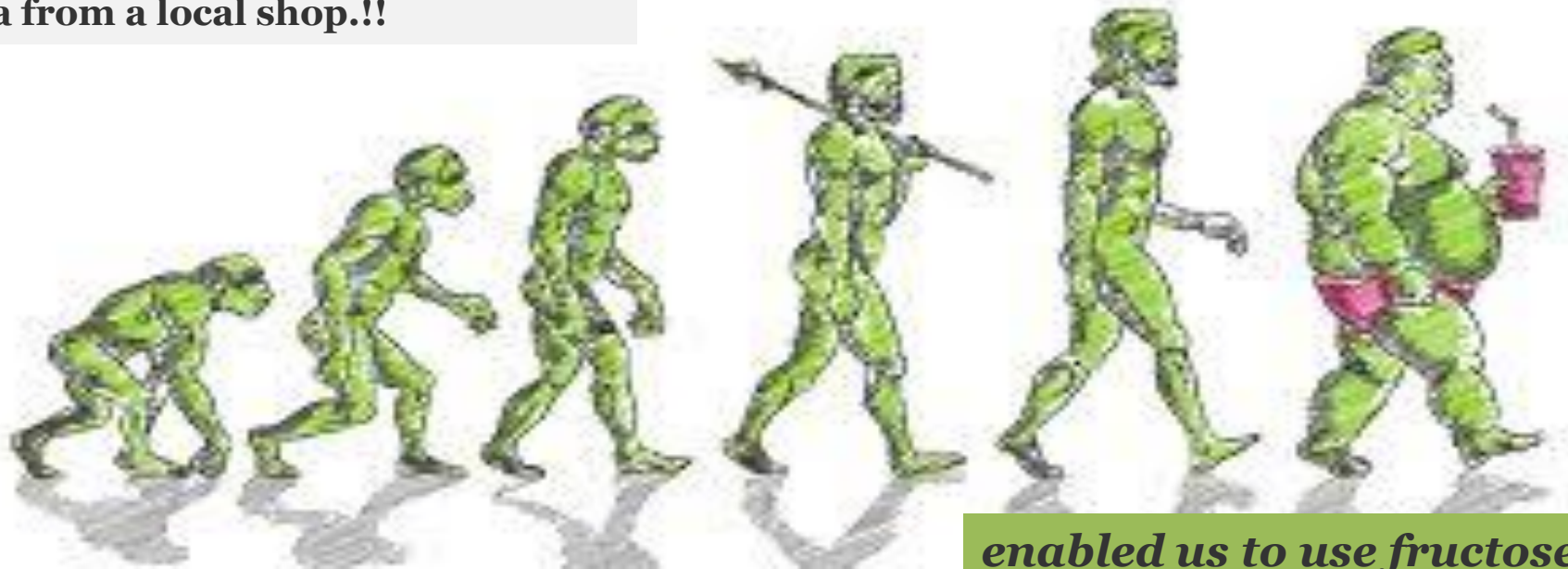
***is it Causal or representative are two conditions***



***Biological Mechanisms for Hyperuricaemia Induced Hypertension***



a time when you could not order a pizza from a local shop.!!



*enabled us to use fructose to accumulate layers of fat which helped us to stay alive during the long cold winters*

- ❑ *our simian ancestors underwent two forever loss-of-function gene mutations, one mutation (30-40 million years ago) wiping out our ability to synthesize Vitamin C,*
- ❑ *the other mutation (10-15 million years ago) undermining our ability to degrade uric acid.*

*Back then, these mutations together :*

# *Uric acid and hypertension*



*story of uric acid*



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*Evidence from Epidemiological studies*



*Causal or representative are two conditions*

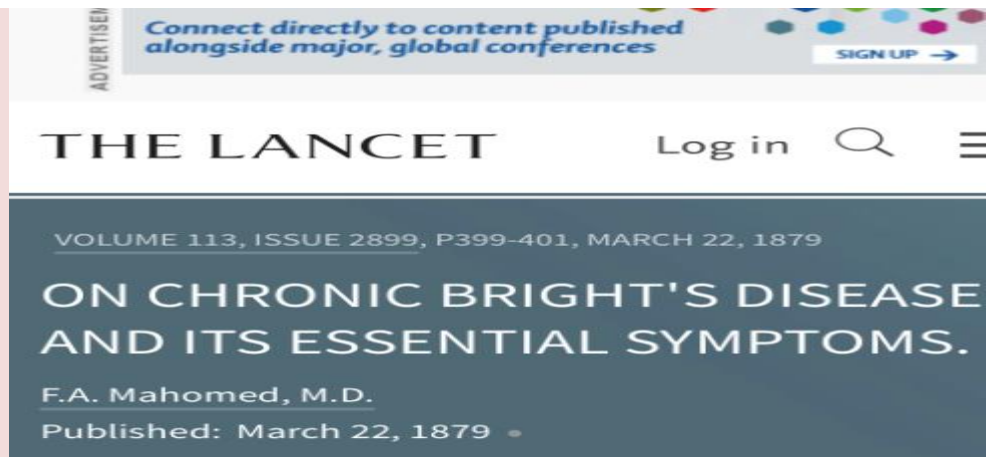


*Biological Mechanisms for Hyperuricaemia Induced Hypertension*



The first link between hypertension (HT) and uric acid (UA) was hypothesized in the 1870s in gout patients

a paper published in the Lancet in 1879 noted that many gout patients were hypertensive



and a subsequent BMJ review of "arterial tension" in 1889 recommended a low purine diet for the management of hypertension

On uric acid and arterial tension

A Haig

*British medical journal* 1 (1467), 288, 1889

# *Uric acid and hypertension*



*story of uric acid*



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*Evidence from Epidemiological studies*



*Causal or representative are two conditions*



*Biological Mechanisms for Hyperuricaemia Induced Hypertension*

# *Evidence from Epidemiological studies*



**Scientific Newsletter**  
Update on Hypertension Management

2018, 19, nr. 69

URIC ACID AND HYPERTENSION: AN UPDATE

***In 1966, it appeared that 47% of hypertensive population was hyperuricemic***

## Plasma Uric Acid and Hypertension in a Chinese Community: Prospective Study and Metaanalysis

**weili ZANg et al :**

*conducted a community-based prospective cohort study comprising 7220 participants (mean age 37 years; 73.8% men) who were free from hypertension at study entry in 1999–2000.*

*During 4-year follow-up, 1370 men (19.0%) and 208 women (11.0%) had developed hypertension*

Article in [Clinical Chemistry](#) 55(11):2026-34 · September 2009



# *Evidence from Epidemiological studies*

*age*

*Sex*



# determining Relationship between uric acid and blood pressure in different age groups

## Multivariate linear regression analysis between blood pressure and uric acid

Lee JJ et al,

A total of 45,098 Koreans who underwent health examinations at Korea Association of Health Promotion with no history of taking drugs related with UA and/or BP

From: [relationship between uric acid and blood pressure in different age groups](#)

Groups	Men						Women					
	SBP			DBP			SBP			DBP		
	$\beta$	$R^2$	p value	$\beta$	$R^2$	p value	$\beta$	$R^2$	p value	$\beta$	$R^2$	p value
Total	0.33	0.10	<0.001	0.39	0.10	<0.001	0.61	0.19	<0.001	0.60	0.14	<0.001
<40 years	0.25	0.09	0.002 ←	0.40	0.09	<0.001 ←	0.54	0.05	<0.001 ←	0.65	0.04	<0.001 ←
40–59 years	0.29	0.06	0.03	0.43	0.05	<0.001 ★	0.44	0.12	0.04	0.51	0.09	<0.001 ←
≥60 years	0.57	0.05	<del>0.05</del>	0.34	0.03	<del>0.08</del>	-0.67	0.07	<del>0.12</del>	-0.26	0.04	<del>0.95</del>

Adjustment was done with age, diabetes, dyslipidemia, body mass index, and estimated glomerular filtration rate.

SBP systolic blood pressure. DBP diastolic blood pressure.

Clin Hypertens. 2015 Jul 15;21:14. doi: 10.1186/s40885-015-0022-9. eCollection 2015.



# *Evidence from Epidemiological studies*

***But !!***

***There are conflicting data  
from different studies***



# Evidence from Epidemiological studies age

Format: Abstract ▾

[J Hum Hypertens](#). 1994 Sep;8(9):677-81.

## Serum uric acid and hypertension: the Olivetti heart study.

[Jossa F<sup>1</sup>](#), [Farinaro E](#), [Panico S](#), [Krogh V](#), [Celentano E](#), [Galasso R](#), [Mancini M](#), [Trevisan M](#).

✉ **Author information**

<sup>1</sup> Institute of Internal Medicine and Metabolic Diseases, Medical School, University Federico II, Naples, Italy.

**a 23% increase in risk for each 1.0-mg/dl increment in UA mg/dl. (mean age 36 yr). in Josaa *et al***

[J Hypertens](#). 2001 Jul;19(7):1209-15.

## Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey.

[Taniguchi Y<sup>1</sup>](#), [Hayashi T](#), [Tsumura K](#), [Endo G](#), [Fujii S](#), [Okada K](#).

**20% increase in risk for each 1.0-mg/dl increment in UA . (mean age 41 yr) Taniguchi *et al***

Format: Abstract ▾

Send to

[Hypertension](#). 2005 Jan;45(1):28-33. Epub 2004 Nov 29.

## Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence.

[Sundström J<sup>1</sup>](#), [Sullivan L](#), [D'Agostino RB](#), [Levy D](#), [Kannel WB](#), [Vasan RS](#).

**a 13% increase in risk for each 1.0-mg/dl increment in UA (mean age 48.7 yr), Sandstorm *et al*.**

# *Age and uric acid in conclusion :*

*The association between SUA levels and prehypertension also*

***decreased with increasing subject age.***

*This association appeared to be no longer significant in elderly populations. In the age-stratified analyses*



# *Evidence from Epidemiological studies*

*age*

*Sex*





## Evidence from Epidemiological studies

# Sex & age

[Grayson PC](#), [Kim SY](#), [LaValley M](#), [Choi HK](#).

### a systematic review and meta-analysis.

*A total of 18 prospective cohort studies representing data from 55,607 participants were included.*

*Hyperuricemia was associated with an increased risk for incident hypertension*

*(adjusted risk ratio [RR] 1.41, 95% confidence interval [95% CI] 1.23-1.58). For a 1 mg/dl*

*increase in uric acid level,*

*the pooled RR for incident hypertension after adjusting for potential confounding was 1.13 (95% CI 1.06-1.20). These effects were significantly larger in **younger** study populations ( $P = 0.02$ ) and **tended to be larger in women** ( $P = 0.059$ ).*

[Arthritis Care Res \(Hoboken\). 2011 Jan; 63\(1\): 102–110. doi: 10.1002/acr.20344](#)

## SUA levels and prehypertension risk based on gender

DE GRUYTER

Clin Chem Lab Med 2016; 20p

Review

Menglin Jiang, Dandan Gong and Yu Fan\*

**Serum uric acid levels and risk of prehypertension:  
a meta-analysis**

***The findings of Menglin Jiang, Dandan Gong and Yu Fan\* study indicated that elevated SUA levels are an independent risk factor for prehypertension after controlling for the potential established risk factors both in men and women.***

***Subgroup analyses based on the region and gender***

***indicated that hyperuricemia appeared to increase the risk of prehypertension in American men but not the women***

# SUA levels and prehypertension risk based on gender



A Cross-Sectional Study 2019 Feb

Int J Endocrinol. 2019; 2019: 7545137.  
Published online 2019 Feb 28. doi: [10.1155/2019/7545137](https://doi.org/10.1155/2019/7545137)

PMCID: PMC6421730  
PMID: [30944567](https://pubmed.ncbi.nlm.nih.gov/30944567/)

## Gender- and Age-Specific Differences in the Association of Hyperuricemia and Hypertension: A Cross-Sectional Study

Xiaoyun Lin,<sup>1</sup> Xiqian Wang,<sup>2</sup> Xin Li,<sup>3</sup> Lili Song,<sup>3</sup> Zhaowei Meng,<sup>001</sup> Qing Yang,<sup>4</sup> Wenjuan Zhang,<sup>4</sup> Yuxia Gao,<sup>4</sup> Zhenwen Yang,<sup>4</sup> Heng Cai,<sup>4</sup> Bo Bian,<sup>4</sup> Yongle Li,<sup>4</sup> Xuefang Yu,<sup>4</sup> Xin Du,<sup>4</sup> Shaopeng Xu,<sup>4</sup> Jing Nie,<sup>4</sup> Ming Liu,<sup>5</sup> Jinhong Sun,<sup>6</sup> Qing Zhang,<sup>6</sup> Ying Gao,<sup>6</sup> Kun Song,<sup>6</sup> Xing Wang,<sup>6</sup> Li Zhao,<sup>7</sup> and Yaguang Fan<sup>006</sup>

[Xiaoyun Lin,](#)

[Author information](#) · [Article notes](#) · [Copyright and License information](#) [Disclaimer](#)

*A total of 78596 ostensibly healthy subjects (47781 men and 30815 women)*

***Men with hyperuricemia (particularly in middle age) had a significantly increased susceptibility of hypertension, while this significant association was not observed in women.***

# *sex and uric acid in conclusion :*

*There are conflicting data  
from different studies*

*may be explained by the different genetic and cultural factors or  
hormonal replacement use between Chinese and Western women*

# *Is there dose dependent relationship between uric acid and incident of HTN ?*



# Is there dose dependent relation sheep between uric acid and incident of HTN ? 2

Sundström J, et al.  
Hypertension. 2005

## Relations of Serum Uric Acid to Longitudinal Blood Pressure Tracking and Hypertension Incidence

Johan Sundström, Lisa Sullivan, Ralph B. D'Agostino, Daniel Levy, William B. Kannel, and Ramachandran S. Vasan

Originally published 29 Nov 2004 | <https://doi.org/10.1161/01.HYP.0000150784.92944.9a> | Hypertension. 2005;45:28–33

[Other version\(s\) of this article](#) ✓

*investigated 3329 Framingham Study participants (mean age 48.7 years; 55.6% women) free of hypertension, myocardial infarction, heart failure, renal failure, or gout.*

*At follow-up 4 years from baseline, 458 persons (13.8%) had developed hypertension, and 1201 persons (36.1%) had experienced progression to a higher BP stage.*

***a 1 SD higher serum UA was associated with an odds ratio (OR) of 1.17 (95% confidence interval [CI], 1.02 to 1.33) for developing hypertension, and an OR of 1.11 (95% CI, 1.01 to 1.23) for BP progression***

# *Is there dose dependent relation sheep between uric acid and incident of HTN ?*

NCBI Resources How To

PMC

US National Library of Medicine  
National Institutes of Health

PMC

Advanced Journal list

Journal List > PLoS One > v.9(12); 2014 > PMC4250178



*PLoS One*. 2014; 9(12): e114259.

Published online 2014 Dec 1. doi: [10.1371/journal.pone.0114259](https://doi.org/10.1371/journal.pone.0114259)

PMCID: PMC4250178

PMID: [25437867](https://pubmed.ncbi.nlm.nih.gov/25437867/)

## Hyperuricemia and Risk of Incident Hypertension: A Systematic Review and Meta-Analysis of Observational Studies

Ji Wang,<sup># 1</sup> Tianqiang Qin,<sup># 1</sup> Jianrong Chen,<sup>1</sup> Yulin Li,<sup>2</sup> Ling Wang,<sup>3</sup> He Huang,<sup>4</sup> and Jing Li<sup>1,\*</sup>

**Ji Wang et al**

***A systematic review and meta-analysis of 18 prospective cohort studies revealed that a 1 mg/dl increase in UA level was associated with an increased risk of incident HT by 13% (pooled RR = 1.13).  
These effects were significantly larger in women and in younger population***

17<sup>th</sup>

International Congress of Nephrology, Dialysis, and Transplantation

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Tabriz, Iran 19-22 November 2019



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# *dose dependent relation sheep in conclusion*

*it seems that there is a dose  
relationsheep but it should be  
cleared with more studies*

# *Uric acid and hypertension*



*story of uric acid*



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*Evidence from Epidemiological studies*



*Causal or representative are two conditions*

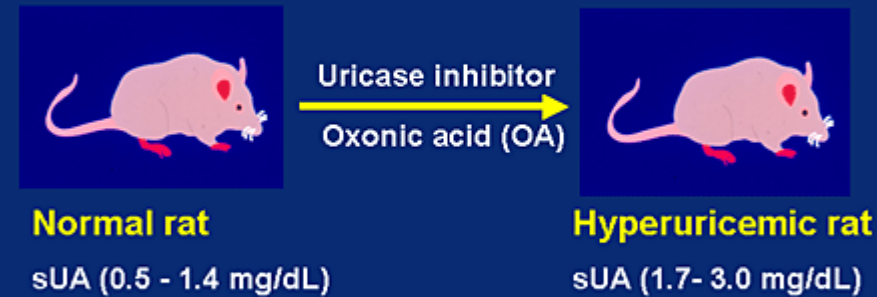


*Biological Mechanisms for Hyperuricaemia Induced Hypertension*

# Biological Mechanisms for Hyperuricaemia Induced Hypertension

*The first animal models of hyperuricaemia were developed in the 1990's by Johnson et al and used oxonic acid as an uricase inhibitor.*

## A Model of Mild Hyperuricemia



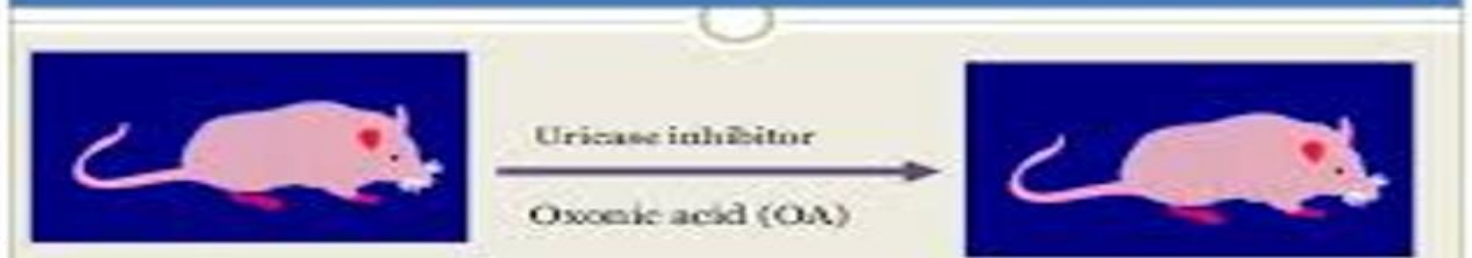
Mazzali et al. *Hypertension*. 2001;38:1101-1106.

*after 2 weeks exposure to mild increases in urate levels there was activation of the renin angiotensin system and decrease in plasma nitrates leading to vasoconstriction and hypertension*

Jennings et al., *J Hypertens* 2014, 3:4  
DOI: 10.4172/2167-1095.1000164



## A Model of Chronic Hyperuricemia



***This hypertension was reversible by***

***either stopping the oxonic acid (allowing the uricase enzyme to function normally) or***

***by lowering urate levels with either xanthine oxidase inhibitors or uricosuric agents.***

***This early hypertension was also responsive to treatment with blockade of the renin-angiotensin system***

Jennings et al., J Hypertens 2014, 3:4  
DOI: 10.4172/2167-1095.1000164

**Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism.**

[Mazzali M](#)<sup>1</sup>, [Hughes J](#), [Kim YG](#), [Jefferson JA](#), [Kang DH](#), [Gordon KL](#), [Lan HY](#), [Kivlighn S](#), [Johnson RJ](#).



***Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 weeks***

**control rats remained normotensive**

***The development of hypertension was prevented by concurrent treatment with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone),***

# *dose dependent relation sheep between uric acid and incident of HTN*



***. A direct relationship was found between blood pressure and uric acid ( $r=0.75$ ,  $n=69$ ), with a 10-mm Hg blood pressure increase for each 0.03-mmol/L (0.5-mg/dL) incremental rise in serum uric acid***

2002) Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol 282: F991-997.

# *Uric acid and hypertension*



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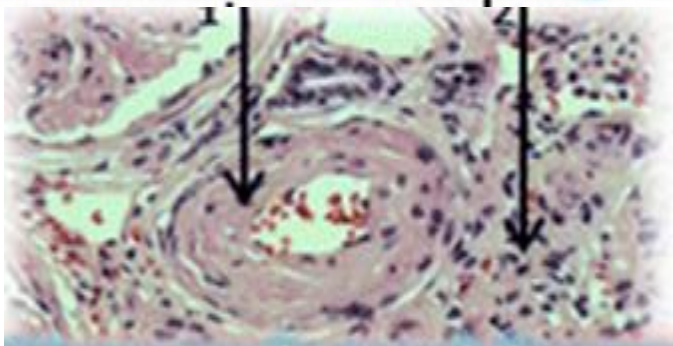


*Biological Mechanisms for Hyperuricaemia Induced Hypertension*

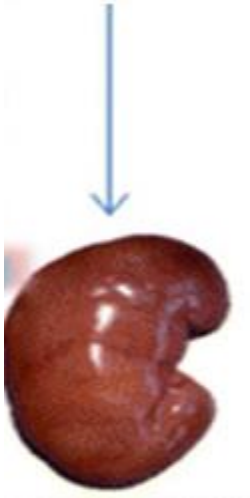
# ↑↑ Uric Acid

↑↑  
Angiotensin II  
Nitric Oxide availability

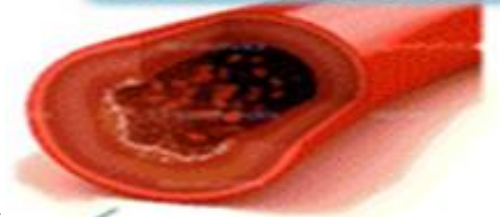
↑↑  
Angiotensin II  
Nitric Oxide availability



Endothelial dysfunction



Atherosclerosis



Hypertension secondary to microvascular renal disease

# *events have led to the reappraisal of the role of uric acid in hypertension*

- ❑ *uric acid might induce hypertension via reducing nitric oxide*
- ❑ *activation of renin-angiotensin system*
- ❑ *causing smooth muscle cell proliferation*
- ❑ *production of various inflammatory mediators PPT-5*

[Arthritis Care Res \(Hoboken\). 2011 Jan; 63\(1\): 102–110.](#)

doi: [10.1002/acr.20344](https://doi.org/10.1002/acr.20344)



## *Undoubtedly the effect of hyperuricaemia in the human body is complex*

*At present evidence is accumulating that hyperuricaemia could be a significant factor in the development of hypertension in some people and importantly, hyperuricaemia is also a potentially reversible risk factor*





## *unanswered question*

*whether aggressive management of hyperuricaemia can reduce blood pressure and improve cardiovascular outcomes significantly enough to be cost effective and outweigh the potential side effects of the urate lowering therapies required. ?*



**. Large randomised controlled trials are needed to answer this question.**

*is possible that in the future management of hyperuricaemia will be as routine as management of cholesterol in the context of modifying cardiovascular risk*





**THANK YOU**  
**FOR YOUR ATTENTION**

**17<sup>th</sup>** International Congress of Nephrology, Dialysis, and Transplantation

Tabriz, Iran 19-22 November 2019



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# ABBASABAD BEHSHAHR



**THANK YOU**  
FOR YOUR ATTENTION





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# ۹ ابان

اسلایدهایی را که کامل حذف کردم قبل عکس  
گذاشتم

# *Normal Uric acid levels*

*.Normal Uric acid levels are 2.4-6.0 mg/dL (female)  
and 3.4-7.0 mg/dL (male)*

*Normal values will vary from laboratory to  
laboratory.*

***Higher SUA levels in men than those in women at  
all ages may be attributable to the role of gender-  
related steroid hormones involved in uric acid  
regulation***



1. This is an observational study;  
interventional studies are needed to clarify whether UA-lowering drugs are useful in preventing development of hypertension,  
which will validate the findings of the current investigation.

Why a genetic adaptation 16M years ago may be leading to 21st century obesity



# Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan.

Nagahama K, et al. Hypertens Res. 2004.

[Show full citation](#)

## Screened Cohort in Okinawa, Japan

*of 4,489 individuals (2,927 men and 1,562 women who did not have hypertension and were not currently using antihypertensive medication were examined at the Okinawa from 1997 to 2000* *the results showed that*

*hyperuricemia to be a new predictor of hypertension development in **both men and women.***



# Relationship between uric acid and blood pressure in different age groups

Jae Joong Lee<sup>1</sup>, Jeonghoon Ahn<sup>2</sup>, Jinseub Hwang<sup>2</sup>, Seong Woo Han<sup>3</sup>, Kwang No Lee<sup>1</sup>, Ji Bak Kim<sup>1</sup>, Sunki Lee<sup>1</sup>, Jin Oh Na<sup>1</sup>, Hong Euy Lim<sup>1</sup>, Jin Won Kim<sup>1</sup>, Seung-Woon Rha<sup>1</sup>, Chang Gyu Park<sup>1</sup>, Hong Seog Seo<sup>1</sup>, Dong Joo Oh<sup>1</sup> and Eung Ju Kim<sup>1\*</sup>

*A total of 45,098 Koreans who underwent health examinations at Korea Association of Health Promotion with no history of taking drugs related with UA and/or BP were analyzed for determining the relationship between serum UA and BP.*

*According to the multivariate linear regression analysis between serum UA and BP, in men <40, serum UA was significantly associated with systolic ( $\beta = 0.25$ ,  $p = 0.002$  and diastolic BP ( $\beta = 0.41$ ,  $p < 0.001$ ) after adjustment for age, diabetes, dyslipidemia, BMI, and eGFR*

*However men between the age 40 and 59 showed similar result regarding only diastolic BP ( $\beta = 0.43$ ,  $p < 0.001$ ).*

*The association between serum UA and BP **was stronger in women <40** ( $\beta = 0.54$ ,  $p < 0.001$  for systolic BP;  $\beta = 0.65$ ,  $p < 0.001$  for diastolic BP)*

*and in between 40 and 59 regarding diastolic BP ( $\beta = 0.51$ ,  $p < 0.001$*

*The association was not significant in men and women  $\geq 60$*

[Clin Hypertens](#). 2015 Jul 15;21:14. doi: 10.1186/s40885-015-0022-9. eCollection 2015.

# SUA levels and prehypertension risk based on gender

[Metab Syndr Relat Disord](#). 2012 Jun;10(3):202-8. doi: 10.1089/met.2011.0119. Epub 2012 Feb 7.

[Peng H](#) et al,

- Hyperuricemia and microalbuminuria are separately and independently associated with prehypertension among Chinese Han women.

[Peng H](#)<sup>1</sup>, [Ding J](#), [Peng Y](#), [Zhang Q](#), [Xu Y](#), [Chao X](#), [Tian H](#), [Zhang Y](#).  
Author information

*reported risk of prehypertension based on gender, was comprised of females only.*

[Lotufo PA](#) et al,

[Angiology](#). 2016 Feb;67(2):180-6. doi: 10.1177/0003319715585037. Epub 2015 May 13.

**Serum Uric Acid and Prehypertension Among Adults Free of Cardiovascular Diseases and Diabetes: Baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil).**

[Lotufo PA](#)<sup>1</sup>, [Baena CP](#)<sup>2</sup>, [Santos IS](#)<sup>3</sup>, [Bensenor IM](#)<sup>3</sup>.

*SUA levels were associated with prehypertension among men.*

# Evidence from Epidemiological studies age

[J Hum Hypertens](#). 2009 Feb;23(2):113-21. doi: 10.1038/jhh.2008.104. Epub 2008 Aug 21.

## Serum uric acid level in primary hypertension among Chinese nonagenarians/centenarians.

[Lu Z<sup>1</sup>](#), [Dong B](#), [Wu H](#), [Chen T](#), [Zhang Y](#), [Wu J](#), [Xiao H](#).

. the [Lu Z<sup>1</sup>](#), [Dong B](#) found that serum uric acid level **is not** directly correlated with hypertension among Chinese nonagenarians/centenarians.

they included 832 unrelated Chinese (269 men and 563 women; ranged in

**age from 90 to 108 years !!** (mean, 94.6+/-4.0)). The mean serum uric acid level was 320 micromol

# *Uric and uncontrolled HTN* K-MetS Study



# *Uric and uncontrolled htn K-MetS Study*

Wolters Kluwer **Medicine**  
Medicine (Baltimore). 2016 Jul; 95(28): e4177. PMID: 26956806  
Published online 2016 Jul 18. PMID: 26956806  
doi: [10.1097/MD.0000000000000417](https://doi.org/10.1097/MD.0000000000000417)

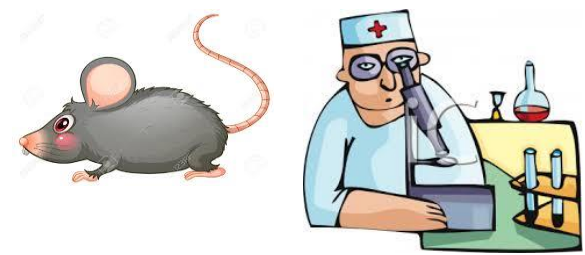
**Hyperuricemia and uncontrolled hypertension in treated hypertensive patients**

*On the 10,601 hypertensive patients who were recruited from 582 private clinics and 11 university hospitals at baseline,*

*.Hyperuricemia predicted uncontrolled hypertension even after 3 months of fimasartan treatment in hypertensive patients*

*Patients without metabolic syndrome had significantly higher odds of uncontrolled hypertension with hyperuricemia (odds ratio, 1.328; 95% confidence interval, 1.007-1.751*

# Kidney pathology



*The kidneys were devoid of urate crystals and were normal by light microscopy.*

*immunohistochemical stains documented an*

- ischemic type of injury with collagen deposition*
- macrophage infiltration*
- an increase in tubular expression of osteopontin*

*Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal NO synthase.*

2002) Hyperuricemia induces a primary renal arteriopathy in rats by a blood pressure-independent mechanism. Am J

Physiol Renal Physiol 282: F991-997

# Effective uric acid-lowering treatment for hypertensive patients with hyperuricemia

[Ohta Y](#)<sup>1,2</sup>, [Ishizuka A](#)<sup>1</sup>, [Arima H](#)<sup>3</sup>, [Hayashi S](#)<sup>1</sup>, [Iwashima Y](#)<sup>1</sup>, [Kishida M](#)<sup>1</sup>, [Yoshihara F](#)<sup>1</sup>, [Nakamura S](#)<sup>1</sup>, [Kawano Y](#)<sup>1</sup>

**20 hypertensive patients with inadequate UA control were administered**

**febuxostat  
40 mg (Feb),**

**benzbromarone  
50 mg  
(Ben)**

**febuxostat 20 mg  
benzbromarone  
25 mg (feb/ben)**

**after 3 months each in a randomized  
modified crossover manner**

**The UA-lowering effects of the low-dose combination of the UA synthesis inhibitor and uricosuric agent were greater than those of the standard dose of each agent alone.**

**uricosuric agent may be more effective at improving vascular function than the UA synthesis inhibitor..**

**Thus, the appropriate management of hyperuricemia with uricosuric drugs appears to be useful for patients with hyperuricemia**

# uric acid

1-uric acid is a waste product created during the normal breakdown of purines

, In humans the final compound of purines catabolism is uric acid. All other mammals possess the enzyme uricase that converts uric acid to allantoin that is easily eliminated through urine

2-naturally occurring substances



*uric acid containing foods such as liver, mushrooms, anchovies, mackerel and dried beans*

**Uric acid is normally cleaned out of the blood by the kidneys, and passes out of the body along with urine**





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# Involvement of Arterial Stiffness and Inflammation in Hyperuricemia-Related Development of Hypertension

Hirofumi Tomiyama □, Kazuki Shiina, Charalambos Vlachopoulos, Yoichi Iwasaki, Chisa Matsumoto, Kazutaka Kimura, Masatsune Fujii, Taishiro Chikamori and Akira Yamashina

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Hypertension. 2018;72:739–745

- *In 3274 Japanese men without hypertension, the brachial-ankle pulse wave velocity, blood pressure, estimated glomerular filtration rate, and serum uric acid and CRP (C-reactive protein) levels were measured annually over an 8-year period*
- *. Of these, 474 subjects developed hypertension by the end of the study period*
- *Hyperuricemia at the study baseline was associated with a significant odds ratio for the development of hypertension by the end of the study period.*



# Uric and uncontrolled htn K-MetS Study

***Of the 10,601 hypertensive patients who were recruited from 582 private clinics and 11 university hospitals at baseline,***

***Hyperuricemia increased the risk of uncontrolled hypertension after 3 months of fimasartan medication (odds ratio, 1.247; 95% confidence interval, 1.063-1.462).***

***Males in the highest quartile of uric acid level were at a 1.322 (95% confidence interval, 1.053-1.660) times higher risk of uncontrolled hypertension in reference to the lowest quartile***

***the same analyses in females were not significant.***

***Patients without metabolic syndrome had significantly higher odds of uncontrolled hypertension with hyperuricemia (odds ratio, 1.328; 95% confidence interval, 1.007-1.751)***

***.Hyperuricemia predicted uncontrolled hypertension even after 3 months of fimasartan treatment in hypertensive patients***

Hyperuricemia and  
uncontrolled hypertension in  
treated hypertensive  
patients

**weili ZANg et all :**

**conducted a community-based prospective cohort study comprising 7220 participants (mean age 37 years; 73.8% men)**

**, who were free from hypertension at study entry in 1999–2000. During 4-year follow-up, 1370 men (19.0%) and 208 women (11.0%) had developed hypertension**

***: Participants in the Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia (TwSHHH) who were free of hypertension at baseline recruitment in 2002 (n=3257)***

***During a mean follow-up of 5.41 years, 1119 persons (34.3%) had experienced progression to a higher blood pressure stage and 496 persons (15.2%) had developed hypertension.***

## Plasma Uric Acid and Hypertension in a Chinese Community: Prospective Study and Metaanalysis

**Uric acid concentration as a risk marker for blood pressure progression and incident hypertension: a Chinese cohort study.**

Yang T, et al. Metabolism. 2012.

[Show full citation](#)

# gender-specific trend of prehypertension outcomes

*may be explained by the different genetic and cultural factors or hormonal replacement use between Chinese and Western women.*

*Women in Syamala et al.'s study were in the reproductive period (mean age 34.5–38.1 years) and the low prevalence of prehypertension may be attributed to the beneficial effects of estrogen.*

*In Lotufo et al.'s study*

*approximately 29.7% women received hormone replacement therapy. Hormone replacement therapy has been suggested to reduce SUA levels in postmenopausal women with hyperuricaemia which may subsequently lowered BP levels*

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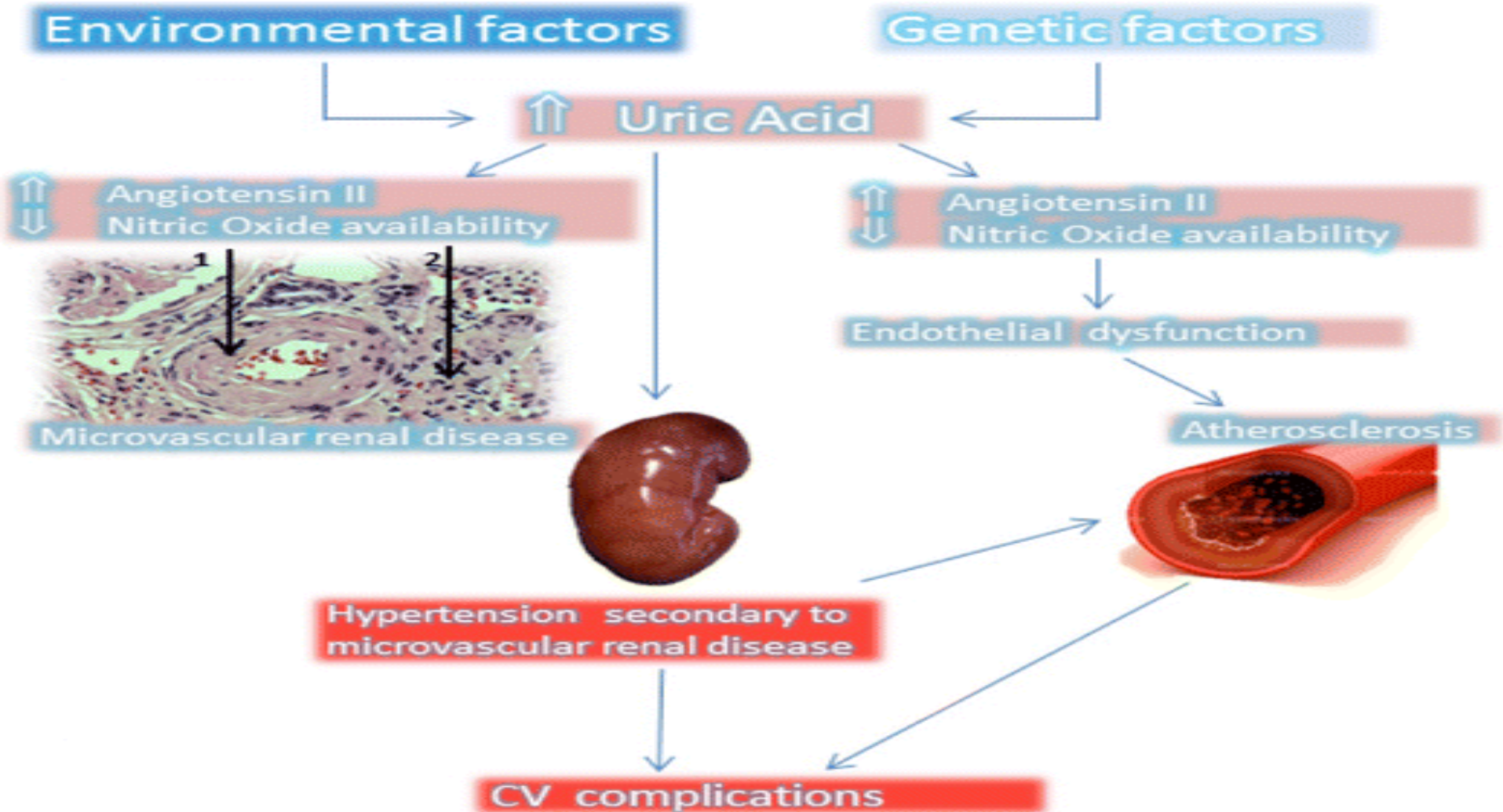
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- *In 3274 Japanese men without hypertension, the brachial-ankle pulse wave velocity, blood pressure, estimated glomerular filtration rate, and serum uric acid and CRP (C-reactive protein) levels were measured annually over an 8-year period*
- *. Of these, 474 subjects developed hypertension by the end of the study period*
- *Hyperuricemia at the study baseline was associated with a significant odds ratio for the development of hypertension by the end of the study period. بین اسلاید در بالا هست ولی پاراگراف پایین حذف شد*
- *After adjustments for covariates, the brachial-ankle pulse wave velocity (estimate= $0.51 \times 10^{-2}$ ,  $P < 0.01$ ) and CRP (estimate=1.91,  $P = 0.03$ ), **but not estimated glomerular filtration rate**, were found to show independent longitudinal associations with the new onset of hypertension*

.,. Hypertension is a significant global health problem and a key contributor to increased risk of cardiovascular events, therefore any intervention that could improve the management of hypertension requires careful examination.



# Biological Mechanisms for Hyperuricaemia Induced Hypertension





## Evidence from Epidemiological studies age

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Epidemiology and Outcomes

## Plasma Uric Acid Level and Risk for Incident Hypertension Among Men

John P. Forman, Hyon Choi and Gary C. Curhan

JASN January 2007, 18 (1) 287-292; DOI: <https://doi.org/10.1681/ASN.2006080865>

### UA level and risk for incident

hypertension was examined prospectively among men who participated in the Health Professionals' Follow-up Study. From among men without hypertension at the time blood was collected, 750 participants who developed hypertension during the subsequent 8 yr and 750 age-matched controls were selected. In addition to adjustment for standard hypertension risk factors and renal function, adjustments controlled for fasting insulin, triglyceride, and cholesterol levels. The mean age of participants was 61 yr, and mean plasma UA level was 6.0 mg/dl (SD 1.25 mg/dl). The multivariable relative risk (RR) for a 1-SD increase in UA was 1.02 (95% confidence interval [CI] 0.87 to 1.18); the RR comparing the highest with lowest quartile of UA was 1.08 (95% CI 0.71 to 1.63). The multivariable RR associated with a 1-SD increase in UA was 1.38 (95% CI 1.05 to 1.81) for men aged <60 yr and 0.90 (95% CI 0.74 to 1.10) for men >60 yr ( $P$  0.04 for interaction). However, further adjustment for fasting insulin, triglyceride, and cholesterol levels attenuated the results (RR for men <60 yr 1.24; 95% CI 0.93 to 1.66). In conclusion, no independent association between UA level and risk for incident hypertension was found among older men

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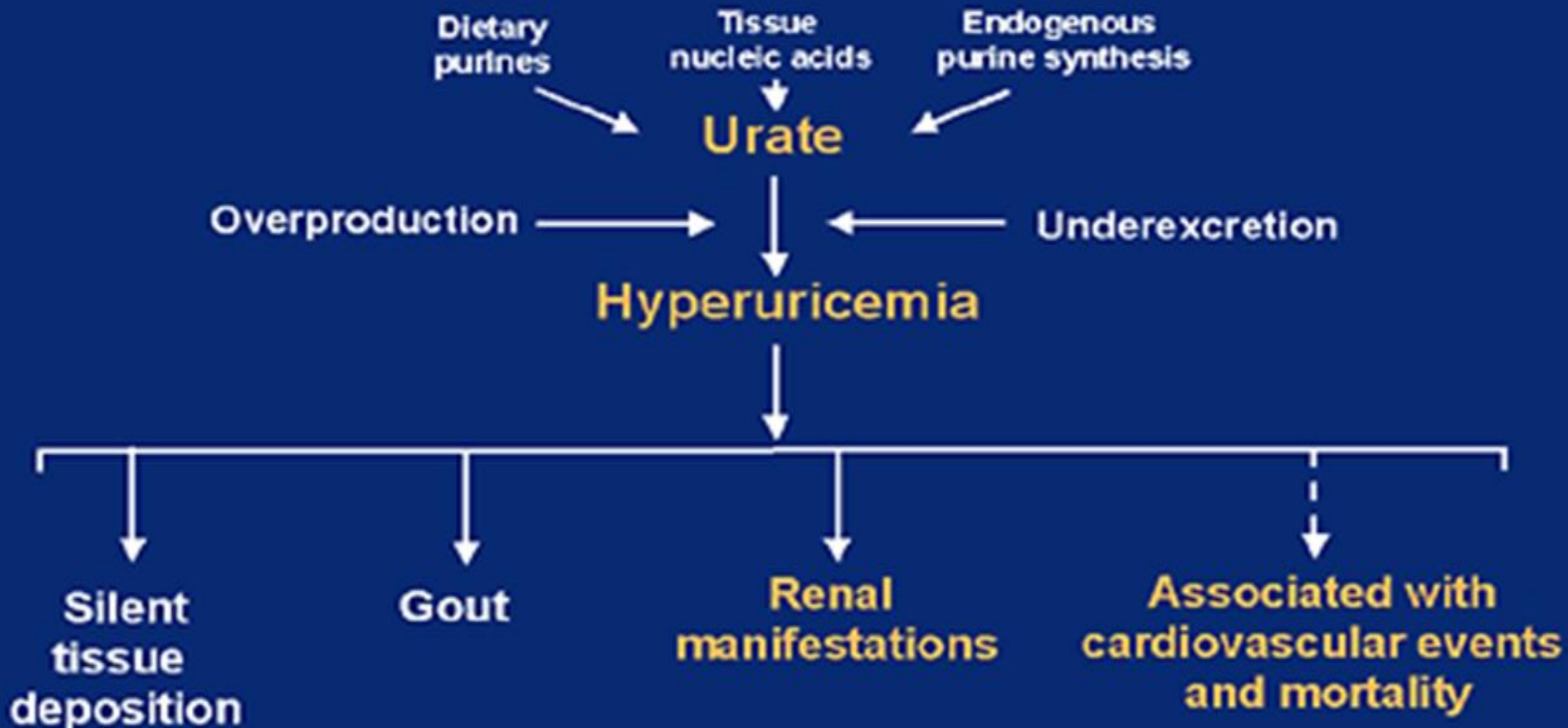
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# The Hyperuricemia Cascade





# Hypertension

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**Hyperuricemia**  
 Does It Matter for the Progression From Prehypertension to Hypertension?  
 Yi-Bang Cheng and Yan Li

Originally published: Dec 2017  
<https://doi.org/10.1161/HYPERTENSIONAHA.117.10443> | [Hypertension](#). 2018;71:09

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- Experimental studies in rats and cells further suggested that the pathophysiologic process of hyperuricemia-induced hypertension might include 2 phases<sup>1</sup>: an initial phase that was driven by uric acid per se and mediated by oxidative stress, inflammation, endothelial dysfunction, and activation of the renin–angiotensin–aldosterone system, and a later phase that was driven by arterial wall hypertrophy and renal microvascular changes and interstitial inflammation but no longer dependent on serum uric acid level ([Figure](#)). These possible mechanisms may explain why the association between hyperuricemia and hypertension is more evident in the young, and the benefit of uric acid lowering in hypertension has only been seen in adolescents.

## 7 Foods that Prevent Gout

Pineapple



Cherry Juice



Hot Peppers

Turmeric



Watercress



Ginger



Lemons

