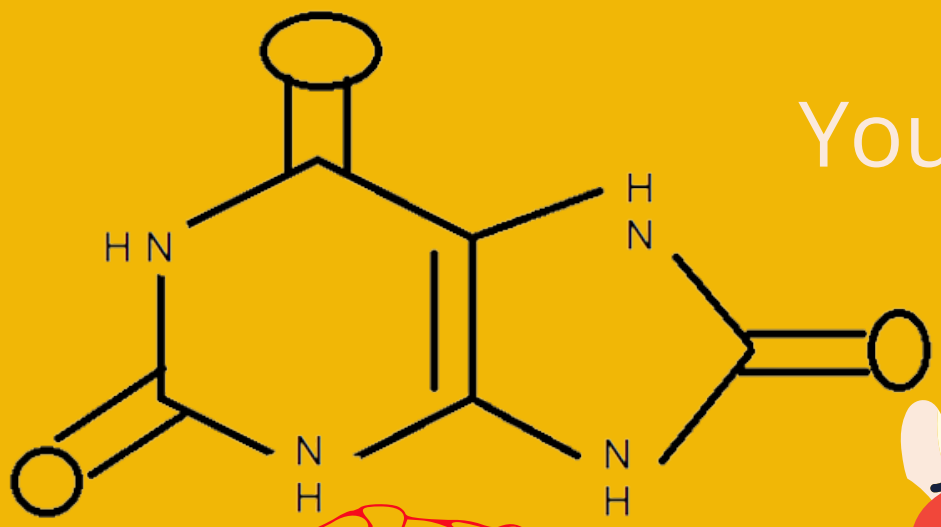
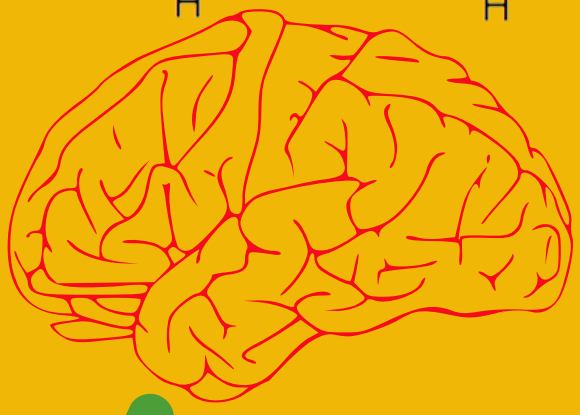
Youri Kruse





Understanding Uric Acid

www.fishybusiness.site

Understanding Uric Acid

Nothing in this book should be seen as advice. You are in control of your own health. Consult with experts if you can.

For more information, visit www.fishybusiness.site

Introduction

Nothing in this booklet should be read at face value. Uric acid is a tricky topic and I am not sure if anybody has understood its full value and potential. This book is my way of trying to understand this molecule and show you that uric acid is not an accidental waste product, but it serves a function. That this function of uric acid can cause harm can be shown, but an important question is whether the harm would be worse without it. When you consider the medical background and culture, one can easily see why uric acid is seen as harmful and dangerous. Uric acid was described as a waste product and was treated as such.

"So far as is known today, uric acid serves no biochemical function in the body other than being an end product of purine metabolism"

SEEGMILLER JE, LASTER L, HOWELL RR. Biochemistry of uric acid and its relation to gout. N Engl J Med. 1963 Mar 28;268:712-6 contd. doi: 10.1056/NEJM196303282681306. PMID: 13987629.

Mostly independent researchers and non-American studies started to show the positive sides(s) of uric acid. I am not trying to say that high uric acid is necessary a good thing. In my opinion it means that there is some kind of distress in the body and increased uric acid is a response to the stress. Chronically high uric acid likely means that the body is not (yet) capable to solve the problem. Reducing uric acid by medications, likely leaves the root problem unresolved.

"This finding is consistent with experimental evidence suggesting that hyperuricemia may be a compensatory mechanism to counteract oxidative damage related to atherosclerosis and aging in humans"

F.Javier Nieto, Carlos Iribarren, Myron D. Gross, George W. Comstock, Richard G. Cutler, Uric acid and serum antioxidant capacity: a reaction to atherosclerosis?, Atherosclerosis, Volume 148, Issue 1, 2000, Pages 131-139, ISSN 0021-9150, https://doi.org/10.1016/S0021-9150(99)00214-2.

Furthermore, many of the problems with uric acid are associations, not the cause. Even though research in many instances equities uric acid in a later stage, the stigma of uric acid stays.

"Results demonstrate that activity within the bilateral hippocampal complex varied with uric acid concentrations. Specifically, activity within the hippocampus and surrounding cortex increased as a function of uric acid level. The current findings suggest that uric acid levels modulate stress-related hippocampal activity."

Goodman AM, Wheelock MD, Harnett NG, Mrug S, Granger DA, Knight DC. The hippocampal response to psychosocial stress varies with salivary uric acid level. Neuroscience. 2016 Dec 17;339:396-401. doi: 10.1016/j.neuroscience.2016.10.002. Epub 2016 Oct 8. PMID: 27725214; PMCID: PMC5118067.

"Studies such as the one presented in the current issue of *Arthritis Research and Therapy* make us realize that uncovering the true nature of apparent simple observations long held true in medicine is seldom straightforward"

Gaffo, A.L., Saag, K.G. Serum urate, menopause, and postmenopausal hormone use: from eminence to evidence-based medicine. *Arthritis Res Ther* **10,** 120 (2008). https://doi.org/10.1186/ar2524

"Among 1,356 men, aged 60 to 69 years when serum uric acid was measured, follow-up for 10 years showed no death from renal failure that was attributable to hyperuricemia."

W.Jeffrey Fessel, Renal outcomes of gout and hyperuricemia, The American Journal of Medicine, Volume 67, Issue 1 1979, Pages 74-82, ISSN 0002-9343, https://doi.org/10.1016/0002-9343(79)90076-7.

Uric Acid

“The plasma urate level in humans (about 300 ILM) is considerably higher than the ascorbate level, making it one of the major antioxidants in humans. Previous work on urate reported in the literature supports our experiments and interpretations, although the findings were not discussed in a physiological context.”

Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci U S A. 1981 Nov;78(11):6858-62. doi: 10.1073/pnas.78.11.6858. PMID: 6947260; PMCID: PMC349151.

One of the most intriguing molecules in health is uric acid. Uric acid is mostly demonized as a harmful molecule but many independent scientists noticed it’s potential. This booklet goes into the good, bad and ugly side of uric acid. Uric acid levels are one of the ways humans are different from most animals. While most animals have uric acid levels of between 0.5 mg/dL, humans boast a 5-6 mg/dL level. Animals quickly convert uric acid into allantoin, with the use of the enzyme uricase. Humans have lost the use of uricase, although we still have the gene for producing the enzyme. The kidneys can get rid of uric acid, but the body holds on to it. With about 90% of uric acid recovered, there must be something more about uric acid.

From the 19th century uric acid was associated with gout, there were however, many different associations, both positive and negative. One such association of uric acid is with motivation and intelligence. The research about uric acid conducted in the 1960s and 1970s became very interesting;

“The major findings in this part were (1) uric acid showed a positive association with grades and with over-achievement (grades adjusted for intelligence quotient); (2) uric acid was positively related to performance on aptitude (speed) tests; (3) a positive association was obtained between uric acid and the "slope" measure of achievement motivation (steepness of gradient of attractiveness ratings of occupations in relation to their difficulty), and a negative association between uric acid and test anxiety.”

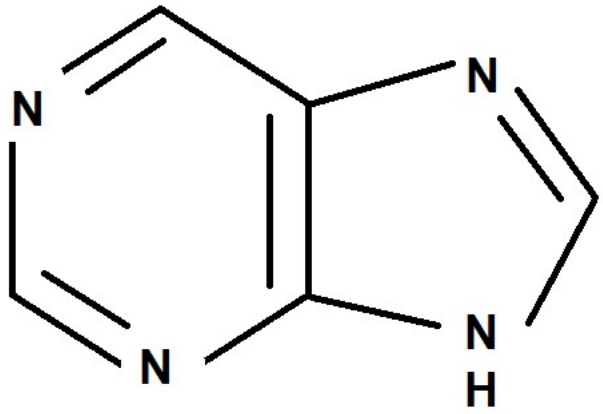
Kasl SV, Brooks GW, Rodgers WL. Serum Uric Acid and Cholesterol in Achievement Behavior and Motivation: I. The Relationship to Ability, Grades, Test Performance, and Motivation. *JAMA.* 1970;213(7):1158–1164. doi:10.1001/jama.1970.03170330040005

“The major findings in this part of the study were (1) Students who are attending college, or are definitely planning to attend, had higher uric acid levels, above and beyond the association with high school grades. (2) There was a positive association between uric acid and activities, irrespective of whether they were the recognized extracurricular activities or the informal social and dating behavior. (3) Subjects with low uric acid levels had more unrealistic vocational expectations and perceptions than did subjects with high uric acid levels”

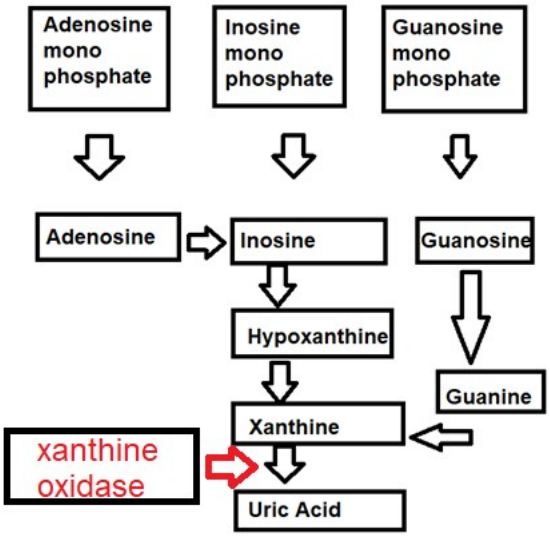
Kasl SV, Brooks GW, Rodgers WL. Serum Uric Acid and Cholesterol in Achievement Behavior and Motivation: II. The Relationship to College Attendance, Extracurricular and Social Activities, and Vocational Aspirations. *JAMA.* 1970;213(8):1291–1299. doi:10.1001/jama.1970.03170340013002

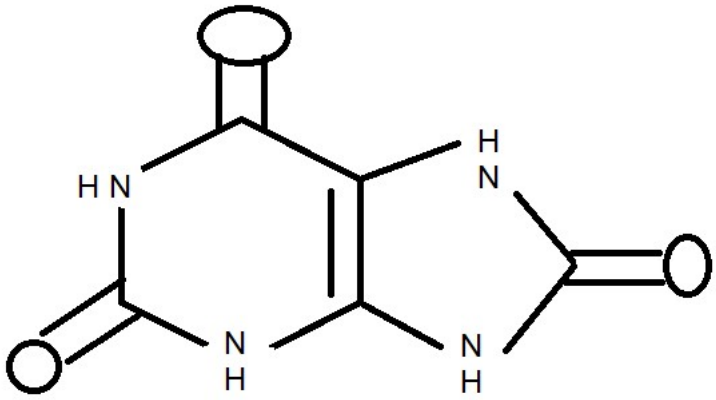
What Is Uric Acid?

Purines are converted into uric acid. Nucleic acid breaks down into the purines, adenine and guanine. Purines include substances that have nitrogenous bases. Other purines of interest are isoguanine, theobromine and caffeine. All of these molecules share a pyrimidine ring and an imidazole ring (see below).



Both adenine and guanine are part of RNA and DNA. Breakdown of these products are metabolized into xanthine. From xanthine it is one step into uric acid by the enzyme xanthine oxidase (XO). The enzyme XO is very important due to its ability to produce inflammatory products. See the pathway below.





URIC ACID

The problem with uric acid is its pathway. Especially the enzyme xantine oxidase (XO) is a potent source of inflammatory products. Most agents against uric acid actually stops xantine oxidase, making these drugs anti-inflammatory, not anti-uric acid. However, by xanthine oxidase inhibition, possible positive effects of uric acid could be missed. Luckely, current day studies focus more on xanthine oxidase as the main target, instead of uric acid. This is important as xanthine oxidase activity is not always correlated with uric aicd levels.

“The emerging picture suggests the increased activity of the enzyme xanthine oxidase (XO) with corresponding increased production of free oxygen radical (ROS) as a main underlying principle with the resulting increase in UA levels being mostly a marker of this up-regulated pathway”

Doehner W, Jankowska EA, Springer J, Lainscak M, Anker SD. Uric acid and xanthine oxidase in heart failure - Emerging data and therapeutic implications. Int J Cardiol. 2016 Jun 15;213:15-9. doi: 10.1016/j.ijcard.2015.08.089. Epub 2015 Aug 11. PMID: 26318388.

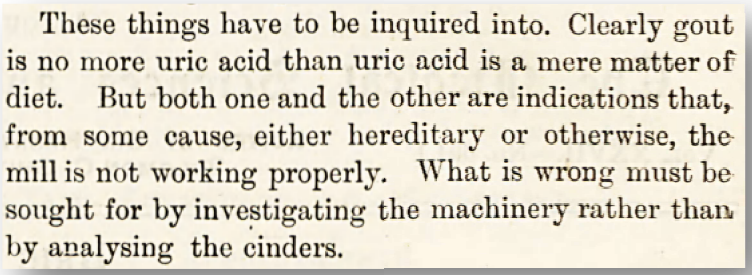
“The value of plasma XO activity was correlated with indices of insulin resistance and the level of circulating liver transaminases. In contrast, the level of serum uric acid was not correlated with indices of insulin resistance. The value of plasma XO activity was not correlated with the serum uric acid level”

Sunagawa S, Shirakura T, Hokama N, et al. Activity of xanthine oxidase in plasma correlates with indices of insulin resistance and liver dysfunction in patients with type 2 diabetes mellitus and metabolic syndrome: A pilot exploratory study. *J Diabetes Investig*. 2019;10(1):94-103. doi:10.1111/jdi.12870

History Of Uric Acid

Although the link between uric acid and gout was established early on, different voices noted that uric acid was a manifestation of a disorder instead of an evil cause. The science articles started to change their stance on uric acid as a new class of drugs (XO inhibitors) were being introduced.

Furthermore uric acid levels decrease as the problem was resolved, as is the case with obesity and uric acid. Obesity is associated with an increased uric acid level, as people lose weight, uric acid is reduced. Another example would be a job loss, as people loss their job, uric acid increased, after a new job was secured, uric acid levels normalized. Uric acid can be seen as a temporary antidote to a stressful situation.



These things have to be inquired into. Clearly gout is no more uric acid than uric acid is a mere matter of diet. But both one and the other are indications that, from some cause, either hereditary or otherwise, the mill is not working properly. What is wrong must be sought for by investigating the machinery rather than by analysing the cinders.

Uric Acid. *Hospital (Lond 1886)*. 1900;27(694):235-236.

“These results indicate that the hyperuricemia of gout may be the result of a variety of metabolic and physiological disturbances. Such a hyperuricemia seems to be a necessary but not a sufficient condition for the subsequent development of gouty arthritis”

SEEGMILLER JE, GRAYZEL AI, LASTER L, LIDDLE L. Uric acid production in gout. *J Clin Invest*. 1961;40(7):1304-1314. doi:10.1172/JCI104360

“It was found that a certain degree of hyperuricaemia existed in normal but obese persons without gout, and that when they lost weight in the course of spa therapy the serum uric acid levels also declined”

Krízek V. Serum uric acid in relation to body weight. *Ann Rheum Dis*. 1966;25(5):456-458.

“Plasma uric acid levels in 35 obese gouty and non-gouty subjects showed a highly significant mean fall of 0.6 mg/100 ml after weight reduction on a low-calorie diet”

Scott JT, Sturge RA. The effect of weight loss on plasma and urinary uric acid and lipid levels. Adv Exp Med Biol. 1977;76B:274-7. doi: 10.1007/978-1-4684-3285-5_41. PMID: 855753.

Anticipation of impending plant shutdown was associated with elevated UA but normal cholesterol levels. (2) Uric acid levels dropped sharply to normal if the men found quick reemployment; otherwise, they remained high till the men were on a new job before showing the same drop.”

Kasl SV, Cobb S, Brooks GW. Changes in Serum Uric Acid and Cholesterol Levels in Men Undergoing Job Loss. *JAMA.* 1968;206(7):1500–1507. doi:10.1001/jama.1968.03150070038006

This notion of uric acid as a reaction to a disturbance was often found. Furthermore high uric acid was found to have some benefits. Current day normal uric acid levels are 2.4-6.0 mg/dL for women and 3.4-7.0 (often 6.8) mg/dL for men. This level is founded upon the idea that molecules containing uric acid stays soluble until this level, and form crystals after. 50 years ago, high uric acid levels without any symptoms were advised to leave it alone until 10 mg. At the same time uric acid was not seen as the primary cause of heart disease.

“Asymptomatic hyperuricemia should be treated only if the plasma uric acid levels are around 10 mg/100 ml or more on several determinations. In addition, patients on a purine-free diet who excrete more than 600 mg uric acid per 24 h should be treated. In both cases, treatment is intended to be prophylactic against gouty nephropathy. At present there is no evidence that primary hyperuricemia alone is a risk factor for early atherosclerosis and especially coronary artery disease. However, more attention should be paid to the accompanying risk factors such as obesity, hyperlipoproteinemia, diabetes mellitus and hypertension”

(ml should be dL, my note)

Siegenthaler-Zuber G. Welcher Harnsäurewert bedarf der Behandlung [Which uric acid value is in need of treatment?]. Schweiz Med Wochenschr. 1976 Apr 3;106(14):487-91. German. PMID: 1265467.

Although high levels above the normal range (above 7-8 mg/dL) are often found to increase mortality (possibly as a co-factor), I often found that within the higher end of the normal range (around 6 mg/dL for men, 5.0 mg/dL for women) uric acid is often associated with better health. I am sure this kind of health can be achieved without high uric acid as long as stress are largely avoid and their thyroid is functioning, and likely as long is iron (especially for men) intake is reduced.

“Higher levels of UA in the physiological range of seminal plasma in the normal group are beneficial to male reproductive health”

Ma, J., Han, R., Cui, T., Yang, C., & Wang, S. (2022). Effects of high serum uric acid levels on oxidative stress levels and semen parameters in male infertile patients. *Medicine*, *101*(3), e28442. https://doi.org/10.1097/MD.0000000000028442

Compared with the high-normal group, participants with lower uric acid levels were associated with poorer cognitive performance during 4-years' follow-up"

Huang Y, Zhang S, Shen J, Yang J, Chen X, Li W, Wang J, Xu X, Xu X, Liu Z, Li X, Ma Y, Yuan C. Association of plasma uric acid levels with cognitive function among non-hyperuricemia adults: A prospective study. Clin Nutr. 2022 Mar;41(3):645-652. doi: 10.1016/j.clnu.2021.12.039. Epub 2022 Jan 1. PMID: 35131717.

"Paradoxically, renal impairment in the presence of chronic hyperuricemia is more often attributable to other factors, such as hypertension or diabetes, rather than serum uric acid concentration itself"

Systemic Uric Acid Administration Increases Serum Antioxidant Capacity in Healthy Volunteers W. Stephen Waring, David J. Webb, and Simon R. J. Maxwell Clinical Pharmacology Unit and Research Centre, Department of Medical Sciences, The University of Edinburgh, Edinburgh, U.K

Uric Acid, Anti-Inflammatory Agent

"In summary, our study suggested that there was a significant positive correlation between UA levels with RBC counts and total hemoglobin concentrations. To the best of our knowledge, this is the first study to report that serum UA levels may be independently associated with RBC parameters. Our findings support the hypothesis that UA plays a beneficial role in RBC longevity."

Song, Tang L, Han J, Gao Y, Tang B, Shao M, Yuan W, Ge W, Huang X, Yao T, Bian X, Li S, Cao W, Zhang H. Uric Acid Provides Protective Role in Red Blood Cells by Antioxidant Defense: A Hypothetical Analysis. Oxid Med Cell Longev. 2019 Mar 27;2019:3435174. doi:

Uric acid is protective for red blood cells carrying oxygen, as is stated in the study above uric acid plays a beneficial role for red blood cell life span. This study is from 2019 and indicated that it is the first study to equate uric acid with red blood cell health (independently). The notion that it took until 2019 to make that conclusion is telling. Uric acid acts as a radical scavenger and as a chelator of metal ions.

The history of uric acid is very much comparable with cholesterol. Cholesterol is also an anti-inflammatory agent, but due to its association with heart disease, is vilified. Both molecules are likely increased with a DHEA deficiency, lowered by estrogen, and both increased cholesterol and uric acid are signs of hypothyroidism and likely somehow compensate for its absence.

Hormones:	
Dehydroepiandrosterone deficiency	**Increased synthesis of fatty acids and cholesterol. Increased purine synthesis**
Thyroid hormone deficiency	**Increased serum cholesterol and uric acid**

Barlow KA. Lipid metabolism in gout. *Proc R Soc Med*. 1966;59(4):325-328.

As cholesterol levels can be lowered by sufficient thyroid hormones, uric acid levels can also be reduced by thyroid. Thyroid can lower uric acid levels in several ways, both by uric acid clearance through the kidneys and by reduced inflammatory products caused by abnormal thyroid function. Inflammation often results in increased uric acid levels. As can be seen in the next table, a thyroid supplement in hypothyroid patients quickly lowers both Thyroid Supporting Hormone (TSH) and lowers high uric acid levels within the normal range. Hypothyroid men are up to 6 times more likely to have gout than men without thyroid

issues, while women with hypothyroidism have more than double the chance of gout.

Table II. Laboratory data in patients (n = 9) with hypothyroidism and hyperuricemia, before and after treatment (2 months) with L-thyroxin (expressed as means ± SD).

Parameter	Pre-treatment	Post-treatment	p
TSH (nv 0.40 - 5.50 mUI/ml)	10 ± 1.2	3.9 ± 1.4	< 0.001
FT4 (nv 7.5 - 15 pg/ml)	3.9 ± 1.2	10.6 ± 2.2	< 0.001
Blood urea (nv 20 - 45 mg/dl)	53 ± 1.9	32 ± 2	< 0.05
Serum creatinine (nv 0.5 - 1.2 mg/dl)	1.9 ± 0.2	0.8 ± 0.2	< 0.05
Creatinine clearance (nv 70 - 120 cc/min)	59 ± 4	101 ± 3	< 0.001
Serum uric acid (nv 3 - 7 mg/dl)	8.5 ± 1.2	5.1 ± 1	< 0.05
Urinary uric acid (nv 300-800\mg/ 24h)	280 ± 17.4	560 ± 15.1	< 0.001

Giordano N, Santacroce C, Mattii G, Geraci S, Amendola A, Gennari C. Hyperuricemia and gout in thyroid endocrine disorders. Clin Exp Rheumatol. 2001 Nov-Dec;19(6):661-5. PMID: 11791637.

These rates were 2.5 times greater in women and 6 times greater in men than found in the controls.. The prevalence of hypothyroidism is significantly increased in patients with aspirate-proven gouty arthritis. Screening for hypothyroidism with an ultrasensitive thyroid stimulating hormone assay should be considered in all patients presenting with gouty arthritis and those with a history of recurrent gouty flares.

Alan R. Erickson, Raymond J. Enzenauer, David M. Nordstrom, John A. Merenich, The prevalence of hypothyroidism in gout, The American Journal of Medicine, Volume 97, Issue 3, 1994, Pages 231-234,ISSN 0002-9343, https://doi.org/10.1016/0002-9343(94)90005-1.

Uric acid is the major antioxidant for humans in the blood. With studies attributing more than 50% of the antioxidant capacity to uric acid, lowering this molecule can have negative consequences. Seeing uric acid as an antioxidant and a protective agent instead of an inducer of damage changes the perception of high uric acid levels. Antioxidants can result in lowering molecules that are bad for health but are needed for survival. One example is nitric oxide (NO). NO can be a substitute for carbon dioxide in the blood and can cause the widening of the arteries in stressful situation. Although NO can be helpful, it is an inflammatory product and causes a lot of problems. Uric acid is known to lower NO, which in turn, can do harm on a short term.

This study shows a potential mechanism by which UA may deplete NO and cause endothelial dysfunction, particularly under conditions of oxidative stress in which UA is elevated and intracellular glutathione is depleted."

Gersch, Christine et al. "Inactivation of nitric oxide by uric acid." *Nucleosides, nucleotides & nucleic acids* vol. 27,8 (2008): 967-78. doi:10.1080/15257770802257952

One study from 1984 found that lowering uric acid levels in people with rheumatoid arthritis, likely create more problems than it solves.

"In 2 patients, flares of the rheumatoid process coincided with normalization of serum urate levels. We propose that persistent hyperuricemia may protect against or decrease the expression of rheumatoid inflammation"

Agudelo CA, Turner RA, Panetti M, Pisko E. Does hyperuricemia protect from rheumatoid inflammation? A clinical study. Arthritis Rheum. 1984 Apr;27(4):443-8. doi: 10.1002/art.1780270412. PMID: 6712758.

Uric acid is a potent scavenger of superoxide; this prevents the formation peroxynitrite (nitric oxide and superoxide). Uric acid has also been found to lower nitric oxide. Beyond lowering nitric oxide levels, uric acid is also involved as a protective agent against glutamate toxicity. It is argued that while humans lost the ability to make vitamin C from glucose, we gained the increase of uric acid from the loss of uricase. Coinciding with the loss of uricase, human lifespan and brain volume increased. When uricase was lost, human lost the ability to create great quantities of allantoin. However, instead of using uricase to convert uric acid to allantoin, human can use toxins and inflammatory products to transform uric acid into allantoin.

"The effect of uric acid was substantially greater than that of vitamin C"

J Cardiovasc Pharmacol. 2001 Sep;38(3):365-71. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. Waring WS, Webb DJ, Maxwell SR.

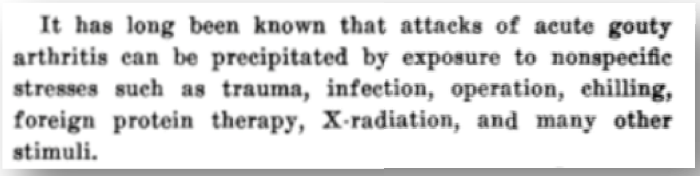
"High UA concentrations are associated with increased serum antioxidant capacity and reduced oxidative stress during acute physical exercise in healthy subjects"

Clin Sci (Lond). 2003 Oct;105(4):425-30. Uric acid reduces exercise-induced oxidative stress in healthy adults. Waring WS, Convery A, Mishra V, Shenkin A, Webb DJ, Maxwell SR

Uric acid administration improved endothelial function in the forearm vascular bed of patients with type 1 diabetes and smokers, suggesting that high uric acid concentrations in vivo might serve a protective role in these and other conditions associated with increased cardiovascular risk.

Diabetes. 2006 Nov;55(11):3127-32. Uric acid restores endothelial function in patients with type 1 diabetes and regular smokers. Waring WS, McKnight JA, Webb DJ, Maxwell SR

Think Uric Acid, Think Gout?



It has long been known that attacks of acute gouty arthritis can be precipitated by exposure to nonspecific stresses such as trauma, infection, operation, chilling, foreign protein therapy, X-radiation, and many other stimuli.

Hellman L. Production of Acute Gouty Arthritis by Adrenocorticotropin. Science. 1949 Mar 18;109(2829):280-1. doi: 10.1126/science.109.2829.280. PMID: 17775053.

"Moderate elevation of SUA would seem to be neither a necessary nor a sufficient cause of gout and there are, as has been indicated, many causes of moderate elevation of SUA.. Theorists have appreciated the importance of such a situation for years but, because it is uncomfortable and scientifically untidy, we have tended to do lip service to it but to ignore it when we can"

Acheson RM. Epidemiology of serum uric acid and gout: an example of the complexities of multifactorial causation. *Proc R Soc Med*. 1970;63(2):193-197.

The idea that high uric acid is the sole cause of gout should have been to rest in the 1960s. As the author rightfully writes, uric acid levels are not a sufficient cause of gout, and many scientists are happy to ignore this. During the 1960s, observations showed different populations with elevated uric acid levels but a huge different in gout numbers. The same scientist noted;

"Confirmatory evidence that elevated SUA in a population does not necessarily precipitate gout can be found by contrasting two of the groups, which have been studied in Australasia, among which SUA levels are higher than is usual. In the New Zealand Maori male with a mean SUA of 6.21 mg/100 ml .. gout is common .. but in the male Australian aborigine in one tribal sample with a mean SUA of 6.03 mg/100 ml it is extremely rare"

Acheson RM. Epidemiology of serum uric acid and gout: an example of the complexities of multifactorial causation. *Proc R Soc Med*. 1970;63(2):193-197.

Allopurinol

Due to the persistence of the medical community to think in one cause for a sickness, a simple mantra became a creed. Allopurinol (a xanthine oxidase suppressor), introduced in 1963-4, seemed to showed benefit at the time. Later studies showed that allopurinol comes with side-effects, many of them, not shared with the public. Allopurinol sales increased dramatically and within 15 years of its launch, it was within the top 60 of most frequently dispensed drugs by community pharmacies in the USA.

“More severe reactions, including exfoliative dermatitis or toxic epidermolysis, eosinophilia with interstitial nephritis or vasculitis, hepatic granulomas, and bone marrow depression have been described in about 350 patients,.. with a further 250 unpublished cases (G Lovett, personal communication). ..Because of the very occasional disastrous reaction the use of allopurinol is not recommended in the many people with mild symptomless hyperuricaemia”

Cameron JS, Simmonds HA. Use and abuse of allopurinol [published correction appears in Br Med J (Clin Res Ed) 1987 Aug 8;295(6594):350]. *Br Med J (Clin Res Ed)*. 1987;294(6586):1504-1505. doi:10.1136/bmj.294.6586.1504

Some research shows that there was an increased of gout caused by pharmaceutical drugs. For example diuretics, like thiazide, were introduced in the 1950s to treat hypertension. Thiazine causes sodium and other minerals to get depleted, and uric acid and gout attacks to be increased. The industry saw one problem and turned it into an opportunity. The rise in uric acid (and other issues, like depletion of potassium), caused by thiazide was simply an opportunity to treat these newly found patients with allopurinol.

“Allopurinol will prevent a rise in the serum uric acid level in thiazide-treated patients and will restore to normal any rise in serum uric acid produced by them”

Rapado A. Allopurinol in thiazide-induced hyperuricaemia. Ann Rheum Dis. 1966 Nov;25(6 Suppl):660-6. doi: 10.1136/ard.25.Suppl_6.660. PMID: 5958696; PMCID: PMC2453404.

In good pharmaceutical fashion, the scientists would blame the genes.

“in gouty patients, increased frequency of attacks of gout may preclude the use of thiazides, or the disease may beeome evident for the first time in a patient who presumably has an inherited metabolic defect”

Dangers in the Use of Some Potent Drugs W. B. SPAULDING, M.D., F.R.C.P.[C], F.A.C.P., Toronto 1962

“Thiazide diuretics may precipitate potassium depletion, skin reactions, pancreatitis, blood dyscrasias, gout, diabetes mellitus and hepatic coma”

SPAULDING WB. Dangers in the use of some potent drugs. Can Med Assoc J. 1962 Dec 15;87(24):1275-81. PMID: 13989937; PMCID: PMC1920825.

“Gout has been considered a rare disease in Finland. However, our hospital series of 77 patients from 1952 to 1976 shows a striking increase during the last 8 years. Over those 8 years the number of persons in the whole country receiving prescribed reimbursable medicines for gout and/or hyperuricaemia rose 10-fold, from 218 to 2188. Diuretics were implicated in one-fourth of our patients-all recent cases.”

Isomäki H, v Essen R, Ruutsalo HM. Gout, particularly diuretics-induced, is one the increase in Finland. Scand J Rheumatol. 1977;6(4):213-6. doi: 10.3109/03009747709095452. PMID: 564545.

"Gouty arthritis in females is relatively infrequent, although the sex ratio may be somewhat altered in different races. A positive family history is relatively prevalent among females whose onset of gout is premenopausal. In those patients with a postmenopausal onset, the incidence of diuretic-associated gout is high"

Yü TF. Some unusual features of gouty arthritis in females. Semin Arthritis Rheum. 1977 Feb;6(3):247-55. doi: 10.1016/0049-0172(77)90022-1. PMID: 835022.

"In summary, we found that recent use of thiazide and possibly loop diuretics was associated with a significantly increased risk for recurrent gouty arthritis."

Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y. Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. J Rheumatol. 2006 Jul;33(7):1341-5. Epub 2006 Jun 1. Erratum in: J Rheumatol. 2006 Aug;33(8):1714. PMID: 16758506.

With the introduction of the diuretic and the greater incidence of gout, medicine like allopurinol use was more frequent. More recent studies show that allopurinol is not that helpful and associated with an increase in mortality. The difficulty with gout is to establish the cause of death, whether death is caused due to gout, other complications or possible side effects from uric acid medication. There is however, evidence that allopurinol is to blame. For example, a high dose of allopurinol is associated with an increase in deaths, compared to a lower dose. While another study found a higher survival of gout patients that did not use allopurinol versus those that did.

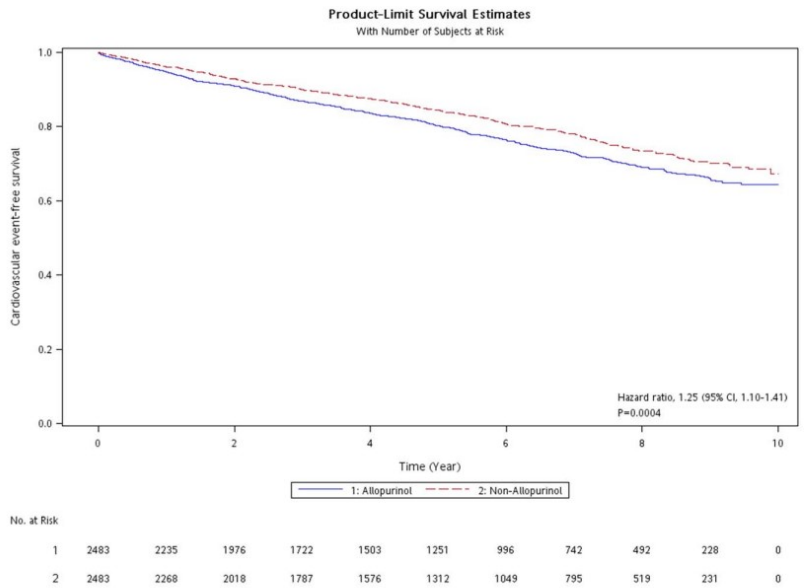


Figure 2. Kaplan-Meier cardiovascular event-free survival curves of gout patients treated with allopurinol and matched comparators of gout patients receiving no allopurinol. At a median follow up of 5.25 years, the allopurinol therapy group harbored an increased hazard ratio of 1.25 (95% confidence interval, 1.10–1.41).
doi:10.1371/journal.pone.0099102.g002

"Using this study design, the results showed an association between allopurinol therapy for gout patients and increased CVD events. Allopurinol may have a harmful effect, with an increase in the risk of CVD even after adjustment for CKD and uremia"

Kok VC, Horng J-T, Chang W-S, Hong Y-F, Chang T-H (2014) Allopurinol Therapy in Gout Patients Does Not Associate with Beneficial Cardiovascular Outcomes: A Population-Based Matched-Cohort Study. PLoS ONE 9(6): e99102. doi:10.1371/journal.pone.0099102

This is the largest study to date to investigate the effects of allopurinol use on mortality and is the first to use a rigorous active-comparator design. Dose escalation was associated with a small (<10%) increase in all-cause mortality, thus showing that a strategy of allopurinol dose escalation, which in current real-life practice is characterized by limited dose increases, is unlikely to improve the survival of patients with gout."

Coburn BW, Michaud K, Bergman DA, Mikuls TR. Allopurinol Dose Escalation and Mortality Among Patients With Gout: A National Propensity-Matched Cohort Study. Arthritis Rheumatol. 2018 Aug;70(8):1298-1307. doi: 10.1002/art.40486. Epub 2018 Jul 8. PMID: 29513934.

"We found that the use of allopurinol and benzbromarone, whether alone or in combination, had a linear dose-response relationship between the numbers of defined daily doses and the risk of CAD, especially in higher DDDs" (DDDs = defined daily doses)

Lin HC, Daimon M, Wang CH, Ho Y, Uang YS, Chiang SJ, Wang LH. Allopurinol, benzbromarone and risk of coronary heart disease in gout patients: A population-based study. Int J Cardiol. 2017 Apr 15;233:85-90. doi: 10.1016/j.ijcard.2017.02.013. Epub 2017 Feb 13. PMID: 28202260.

"Survival of patients treated with allopurinol for hyperuricemia was significantly lower compared with untreated subjects (70.1 vs 77.2 for 1-year survival and 60.3 vs 68.5 for 2-year survival)"

Málek F, Ošťádal P, Pařenica J, Jarkovský J, Vítovec J, Widimský P, Linhart A, Fedorco M, Coufal Z, Miklík R, Krűger A, Vondraková D, Špinar J. Uric acid, allopurinol therapy, and mortality in patients with acute heart failure--results of the Acute HEart FAilure Database registry. J Crit Care. 2012 Dec;27(6):737.e11-24. doi: 10.1016/j.jcrc.2012.03.011. Epub 2012 Jun 12. PMID: 22699032.

About 3% of the western population has gout, the interesting part is the fact that man are about 8 times more likely to have gout than women. More than 10% of the population have higher uric acid levels than deemed healthy. Men have higher serum uric levels than women on average. Women, however, tend to develop a greater incidence of gout, as they age (after menopause). Many studies found that uric acid levels were normal during a gout attack.

"Normal serum uric acid levels were found in 63.3% of the patients with acute gout attack...The low uric acid level is correlated with increased inflammatory factors and urinary excretion of uric acid"

Bădulescu M, Macovei L, Rezuş E. Acute gout attack with normal serum uric acid levels. Rev Med Chir Soc Med Nat Iasi. 2014 Oct-Dec;118(4):942-5. PMID: 25581951.

"Many patients with acute gout (11%-49%) have normal serum uric acid (SUA) levels."

Leiszler M, Poddar S, Fletcher A. Clinical inquiry. Are serum uric acid levels always elevated in acute gout? J Fam Pract. 2011 Oct;60(10):618-20. PMID: 21977490.

Uric acid renal stones may occur in hyperuricemic, hyperuriciuric gouty patients but more often occur in elderly Italian or Jewish patients with normal serum and urinary uric acid levels"

HENNEMAN PH, WALLACH S, DEMPSEY EF. The metabolism defect responsible for uric acid stone formation. *J Clin Invest*. 1962;41(3):537-542. doi:10.1172/JCI104507

Think Gout, Think Iron

Why would men have a higher incidence of gout than women? Why do men have higher levels of uric acid than women? Why is meat associated with increased gout, while dairy is not? Why does the incidence of gout increases for women after menopause?

One possible reason for this could be iron. Iron levels are higher in men than in women; furthermore postmenopausal women have higher iron levels than premenopausal women and have an increased chance of gout. Milk has very limited amounts of iron, while meat has a lot. People with elevated ferritin levels, often have high uric acid levels. As high ferritin levels are pro-inflammatory, uric acid could be seen as an anti-inflammatory remedy. Going into the scientific literature, it shows a huge quantity of studies leading to excess iron as a causal factor in gout. A small compilation of different studies includes;

"This elevation in the production of uric acid with increased concentrations of iron could possibly reflect a response of the host to diminish the oxidative stress presented by available metal as the uric acid assumes the empty or loosely bound coordination sites of the iron to diminish electron transport and subsequent oxidant generation"

Ghio AJ, Ford ES, Kennedy TP, Hoidal JR. The association between serum ferritin and uric acid in humans. Free Radic Res. 2005 Mar;39(3):337-42. doi: 10.1080/10715760400026088. Erratum in: Free Radic Res. 2007 Dec;41(12):1385. PMID: 15788238.

"Their serum iron levels were found to be higher than the controls. Increase in serum iron was directly proportional to the increased levels of uric acid, urea and creatinine….It is suggested that haemolysis may be a major contributory factor for the increased levels of serum iron in pre-eclampsia"

Gupta S, Nanda S, Singh U, Bansal S, Lal H. Evaluation of the changes in serum iron levels in pre-eclampsia. Indian J Clin Biochem. 1997 Dec;12(1):91-4. doi: 10.1007/BF02867964. PMID: 23100872; PMCID: PMC3454039.

"Elevated levels of uric acid is associated with elevated ferritin levels and may serve as a risk stratification variable for presence of iron overload and hemochromatosis"

Mainous AG 3rd, Knoll ME, Everett CJ, Matheson EM, Hulihan MM, Grant AM. Uric acid as a potential cue to screen for iron overload. J Am Board Fam Med. 2011 Jul-Aug;24(4):415-21. doi: 10.3122/jabfm.2011.04.110015. PMID: 21737766.

"Taken together, these results support the hypothesis that iron might be a fundamental factor triggering gouty arthritis in humans as well"

Francesco S. Facchini, Near-iron deficiency-induced remission of gouty arthritis, *Rheumatology*, Volume 42, Issue 12, December 2003, Pages 1550–1555, https://doi.org/10.1093/rheumatology/keg402

“Increased ferritin levels associated with gout and flare frequency. There was evidence of a causal effect of iron and ferritin on urate.”

Fatima, Tahzeeb et al. “The relationship between ferritin and urate levels and risk of gout.” *Arthritis research & therapy* vol. 20,1 179. 15 Aug. 2018, doi:10.1186/s13075-018-1668-y

Gout Crystals

“Gouty inflammation can be suppressed by an iron chelator”

Ghio AJ, Kennedy TP, Rao G, Cooke CL, Miller MJ, Hoidal JR. Complexation of iron cation by sodium urate crystals and gouty inflammation. Arch Biochem Biophys. 1994 Sep;313(2):215-21. doi: 10.1006/abbi.1994.1379. PMID: 8080265.

Gout is often defined as crystal deposits in the joints known as sodium urate crystal. A 1994 study examined the crystals and found significant amounts of iron. The painful flares begin when macrophages are starting to digest the crystals, releasing inflammatory products, leading to painful flares. The observation that crystals were also found in asymptomatic people, leads to the conclusion, that more is needed to explain gout.

“Thus, it appears that hyperuricaemia and/or crystal deposition are not sufficient to cause acute gouty attacks and that some other factor(s) are necessary to trigger the inflammation.”

Francesco S. Facchini, Near-iron deficiency-induced remission of gouty arthritis, *Rheumatology*, Volume 42, Issue 12, December 2003, Pages 1550–1555, https://doi.org/10.1093/rheumatology/keg402

Since the 1960s, the quantity of uric acid and deposits of crystals in the synovial fluid is often used to diagnose gout. At the same time iron deposits were often found in the synovial fluid of people with arthritis. To protect against high iron blood levels, iron gets deposited into the joint. One of the anti-inflammatory functions of uric acid is to form stable products with iron. In this way, iron becomes less inflammatory. There have been observations that gout offers protection against possible worse outcomes. Gout has been associated with a certain protection against other diseases. It is known that people with gout have a lower chance of getting certain diseases, and in some cases, like with multiple sclerosis are mutually exclusive. Women have a greater incidence of multiple sclerosis and a limited incidence of gout.

“gout and multiple sclerosis are mutually exclusive, in that there are no reported cases of multiple sclerosis with gout”

Álvarez-Lario B, Macarrón-Vicente J. Uric acid and evolution. Rheumatology (Oxford). 2010 Nov;49(11):2010-5. doi: 10.1093/rheumatology/keq204. Epub 2010 Jul 13. PMID: 20627967.

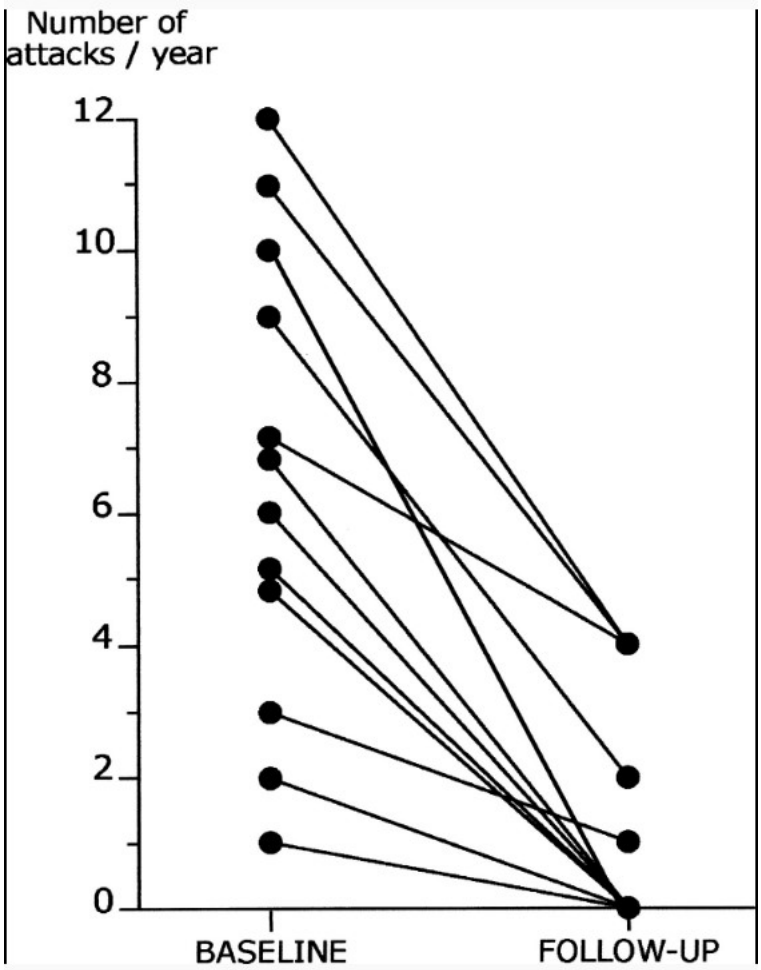
“Histological examination of the synovial membrane has demonstrated that iron deposits are a constant feature of the pathology of rheumatoid arthritis”

Muirden, K. D., & Senator, G. B. (1968). Iron in the synovial membrane in rheumatoid arthritis and other joint diseases. *Annals of the rheumatic diseases*, *27*(1), 38–48. https://doi.org/10.1136/ard.27.1.38

“This unexpected finding supports the suggestion that iron deposition in hemochromatosis is occasionally responsible for a symptomatic arthritis”

KRA SJ, HOLLINGSWORTH JW, FINCH SC. ARTHRITIS WITH SYNOVIAL IRON DEPOSITION IN A PATIENT WITH HEMOCHROMATOSIS. N Engl J Med. 1965 Jun 17;272:1268-71. doi: 10.1056/NEJM196506172722404. PMID: 14290548.

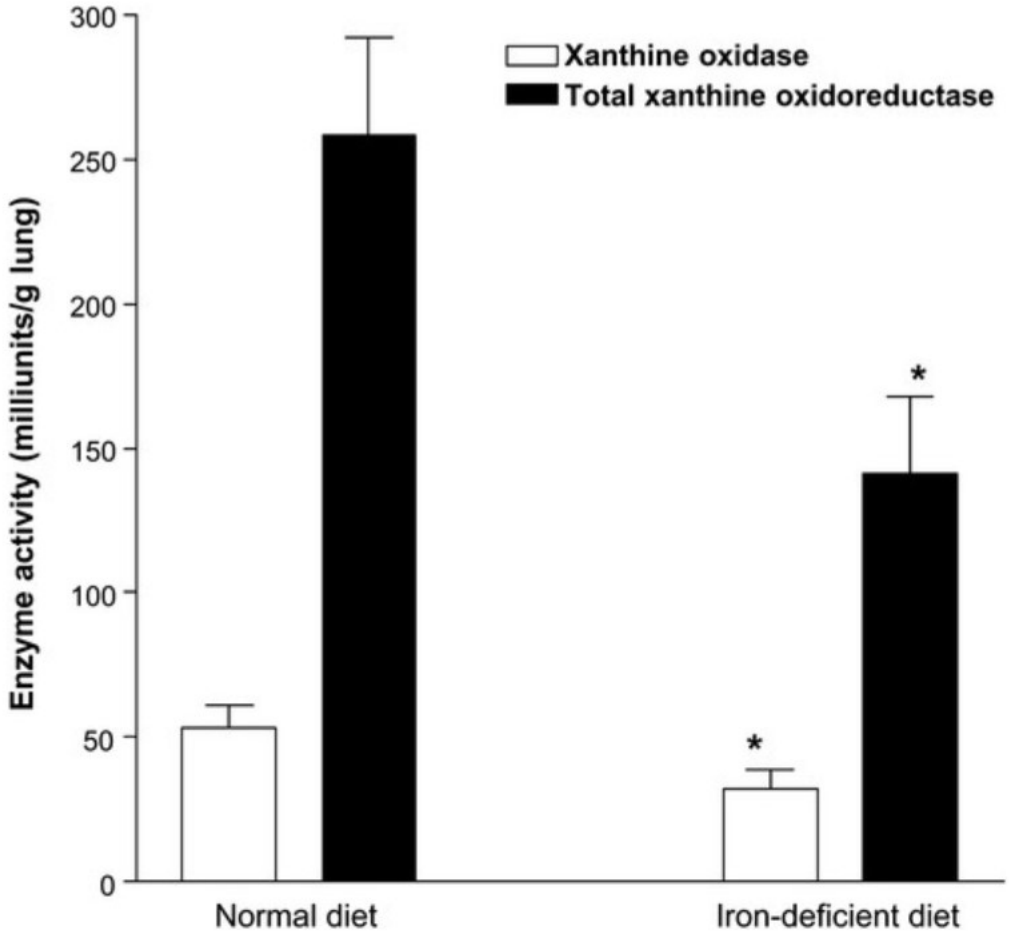
In 1992, 12 patients were selected with high uric acid levels and a history of primary gout. These patients were part of a blood donation (phlebotomies) strategy to lower their iron levels to near iron deficiency levels, but enough to sustain normal red blood cells. The results showed that after 28 months, 58% of patient was in complete remission and a decrease of attacks in the rest of the patients. See the results below.



The intra-individual change in the average number of gouty attack per year decreased from 6.4 ± 3.0 to 2.0 ± 1.0 after achievement of NID ($P < 0.001$). NID= near-iron deficiency (NID) level. Mean attack rate per person per year before (baseline) and after (follow-up) NID.

Francesco S. Facchini, Near-iron deficiency-induced remission of gouty arthritis, *Rheumatology*, Volume 42, Issue 12, December 2003, Pages 1550–1555, https://doi.org/10.1093/rheumatology/keg402

The evidence that iron is involved in gout and elevated uric acid goes beyond its inflammatory properties. The before mentioned enzyme xanthine oxidase requires iron to function. A diet low in iron can reduce the activities of this enzyme. Animal research show that an iron deficient diet severely reduces both xantine oxidase and the enzyme that is used before xanthine oxidase, xanthine oxidoreductase



"These results suggest the possibility that the production of uric acid, a major chelator of iron in extracellular fluid, is directly influenced by iron-mediated regulation of the expression and/or activity of its enzymatic source, xanthine oxidase."

Ghio AJ, Kennedy TP, Stonehuerner J, Carter JD, Skinner KA, Parks DA, Hoidal JR. Iron regulates xanthine oxidase activity in the lung. Am J Physiol Lung Cell Mol Physiol. 2002 Sep;283(3):L563-72. doi: 10.1152/ajplung.00413.2000. PMID: 12169576.

"We conclude that superoxide and hydrogen peroxide, produced from xanthine oxidase, support iron-catalyzed lipid peroxidation through their participation in redox reactions of iron, that is, they facilitate Fe(II) oxidation or Fe(III) reduction necessary for lipid peroxidation. The relevance of the reactions of O2-. and H2O2 on physiological chelates of iron are discussed"

Miller DM, Grover TA, Nayini N, Aust SD. Xanthine oxidase- and iron-dependent lipid peroxidation. Arch Biochem Biophys. 1993 Feb 15;301(1):1-7. doi: 10.1006/abbi.1993.1107. PMID: 8382902.

Gout And Hormones

Women have a greater incidence of low thyroid function (hypothyroid) than men. Gout crystals are in part formed by temperature, the lower the temperature, the quicker crystals are formed. Thyroid hormone regulates in part body temperature. Women have a slightly higher body temperature than women. This could in part explain the higher incidence of gout with men. The low body temperature in hypothyroidism makes gout more likely. Adding thyroid hormone helps against in several ways, both by possible taking over some of the anti-oxidant functions and by increasing temperature. The gout crystals are usually located furthers away from the heart and are the coldest part of the body. As the thyroid hormone warms up the body, crystals are less likely to form.

"On the basis of the preceding observations it is tempting to speculate that the observed predilection of gouty arthritis and gouty tophi for the peripheral parts of the body (extremities, ears, etc) may at least in part be attributed to the fact that these parts are subjected to sustained mean temperatures considerably below 37 °C"

Loeb JN. The influence of temperature on the solubility of monosodium urate. Arthritis Rheum. 1972 Mar-Apr;15(2):189-92. doi: 10.1002/art.1780150209. PMID: 5027604.

Estrogen Saves The Day, Does It?

The medical industry didn't waste any time linking estrogen to protection against gout. The reduced incidence of gout in women was immediately linked to the "female" hormone estrogen, without mentioning progesterone. The estrogen industry plays clever games with the public by confusing terms. By equating estrogen with fertility, estrogen can do no wrong. For years estrogen therapy was given (also to men) for gout. There are multiple studies that find that uric acid is lowered by estrogen, however, estrogen increase iron levels. A very large study from Korea followed the same formula when the article stated;

"Shorter exposure to endogenous estrogen was associated with a high risk of gout"

By equating reproductive life span with availability of estrogen, a misleading conclusion can be reached. Estrogen decreases long after progesterone is decreased. The ratio of progesterone to estrogen decreases before and after menopause, making progesterone a more likely candidate as an anti-gout factor. The same Korean study goes on to state that estrogen therapy is increased with the incidence of gout.

"Use of oral contraceptives (OC) and hormone replacement therapy (HRT) were associated with an increased risk of gout"

Eun, Y., Kim, I. Y., Han, K., Lee, K. N., Lee, D. Y., Shin, D. W., Kang, S., Lee, S., Cha, H. S., Koh, E. M., Lee, J., & Kim, H. (2021). Association between female reproductive factors and gout: a nationwide population-based cohort study of 1 million postmenopausal women. *Arthritis research & therapy*, *23*(1), 304. https://doi.org/10.1186/s13075-021-02701-w

Another reason why progesterone is a better candidate is its ability to warm the body, while estrogen is association with lowering body temperature. Gout attacks are more likely at night or early morning. In men estrogen is slightly higher in the morning, furthermore obesity is a predictor for gout and obese men

have more estrogen than men with a normal weight. Women are likely protected against gout by progesterone. Progesterone causes uric acid to be secreted from the body.

"We administered progesterone to normal women and observed that GFR, uric acid clearance and kallikrein excretion increased significantly"

Atallah AN, Guimarães JA, Gebara M, Sustovich DR, Martinez TR, Camano L. Progesterone increases glomerular filtration rate, urinary kallikrein excretion and uric acid clearance in normal women. Braz J Med Biol Res. 1988;21(1):71-4. PMID: 3179582.

An interestingly study from 2015 showed the difference between opposed estrogen and unopposed estrogen and the incidence of gout. While the opposed group (with a progesterone derivative), had a decreased change of getting gout, the unopposed estrogen group saw a significant increase in the gout incidence. This made the researchers conclude that progesterone might be the protective factor, instead of estrogen.

"Current use of oral opposed oestrogens, but not unopposed oestrogens, was associated with a decreased risk of incident gout in patients without renal failure and was more pronounced in patients with hypertension. The observed risk decrease for gout in users of opposed oestrogens may be explained by the progesterone rather than the oestrogen component"

Bruderer SG, Bodmer M, Jick SS, Meier CR. Association of hormone therapy and incident gout: population-based case-control study. Menopause. 2015 Dec;22(12):1335-42. doi: 10.1097/GME.0000000000000474. PMID: 25968834.

Similar results were found with relation to gallstones (gallstones are also associated with uric acid). While the unopposed women had an increased chance of gallstones compared the group that included progestine (progestine is a synthetic form of progesterone and is not recommended). In this study however, the group of women that never used estrogen (either opposed or unopposed) had the lowest chance of having gallstones.

"Postmenopausal estrogen therapy was associated with increased risk of gallstone disease in current and former estrogen users. Use of unopposed estrogen was associated with higher risk than use of estrogen opposed by progestin"

Poulsen, Maja & Erichsen, Rune & Frøslev, Trine & Rungby, Joergen & Sørensen, Henrik. (2013). Postmenopausal Estrogen Therapy and Risk of Gallstone Disease: A Population-Based Case–Control Study. Drug safety : an international journal of medical toxicology and drug experience. 36. 10.1007/s40264-013-0118-7.

Bone, Brain & Muscle Health & Uric Acid

Bones, the brain and the muscles all atrophy as we age. This atrophy is under the direction of different inflammatory products. These inflammatory products influence our hormones in a negative way and attack our tissues. Uric acid, as a basic anti-inflammatory product, can form a needed antidote. Although most of the evidence is an association, it leaves a clue as to a possible aid in tissue preservation.

"Higher levels of serum UA are associated with higher BMD (at the expense of thicker cortices and narrower bone diameters) and may be a protective factor in bone metabolism"

Muka T, de Jonge EA, Kiefte-de Jong JC, Uitterlinden AG, Hofman A, Dehghan A, Zillikens MC, Franco OH, Rivadeneira F. The Influence of Serum Uric Acid on Bone Mineral Density, Hip Geometry, and Fracture Risk: The Rotterdam Study. J Clin Endocrinol Metab. 2016 Mar;101(3):1113-22. doi: 10.1210/jc.2015-2446. Epub 2015 Dec 18. PMID: 26684274.

"An increased serum UA level is shown to be associated with a lower risk of fracture, albeit additional large, high-quality prospective studies or a meta-analysis of individual data are still needed to verify the association."

Yin P, Lv H, Li Y, Meng Y, Zhang L, Tang P. The association between serum uric acid level and the risk of fractures: a systematic review and meta-analysis. Osteoporos Int. 2017 Aug;28(8):2299-2307. doi: 10.1007/s00198-017-4059-3. Epub 2017 May 9. PMID: 28488134.

Men have less bone disease than women and stronger bones. Uric acid has an interesting association with bone health. A Chinese study found that higher uric acid levels were associated with better bone health. The thickest bones in the group had uric acid levels above the "healthy" cut off levels.

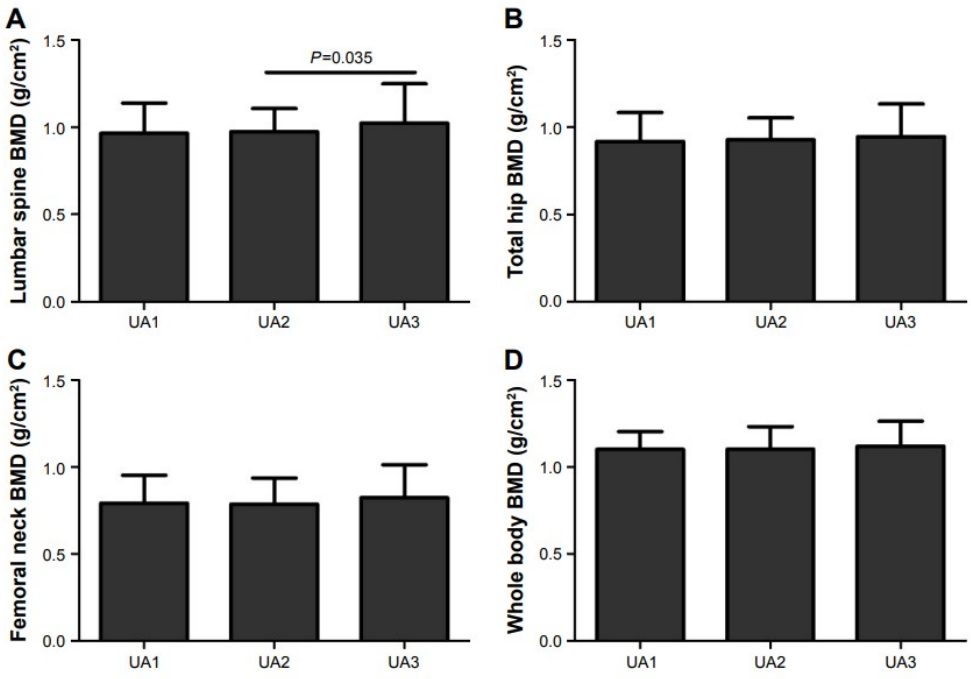


Figure 1 BMD values according to serum uric acid tertiles.
Notes: BMD values in the (**A**) lumbar spine, (**B**) total hip, (**C**) femoral neck and (**D**) whole body were compared among three tertiles of serum uric acid levels using one-way ANOVA. UA1: uric acid concentration <4.7 mg/dL; UA2: 4.7 mg/dL ≤ uric acid concentration <6.0 mg/dL; UA3: uric acid concentration ≥6.0 mg/dL. Error bars represent the standard deviation values.
Abbreviations: ANOVA, analysis of variance; BMD, bone mineral density.

Xiao J, Chen WJ, Feng XH, Liu WY, Zhang ZX, He L, Ye ZB. Serum uric acid is associated with lumbar spine bone mineral density in healthy Chinese males older than 50 years. *Clin Interv Aging*. 2017;12:445-452 https://doi.org/10.2147/CIA.S130690

The protective factor of uric acid could mean the current approach to lower uric acid could have serious negative effects. Within the literature, scientists have argued that the use of uric acid lowering medication (ULM) could have consequences. Since mostly older people take uric acid lowering medication, the situation in the elderly could be made worse by lowering uric acid. Drugs such as allopurinol are associated with an increase in fractures, especially in women.

"Prespecified subanalyses by filled dose of allopurinol (mg/day in first year of prescription) showed increased hip and major fracture risk in women in the highest allopurinol dose grouping only, while a less strong dose effect was evident for fracture rates in men"

Dennison EM, Rubin KH, Schwarz P, Harvey NC, Bone KW, Cooper C, Abrahamsen B. Is allopurinol use associated with an excess risk of osteoporotic fracture? A National Prescription Registry study. Arch Osteoporos. 2015;10:36. doi: 10.1007/s11657-015-0241-4. Epub 2015 Oct 19. PMID: 26481934; PMCID: PMC5384630.

"Higher serum UA concentrations were associated with a lower risk of morphometric VF independently of ULM in Japanese elderly men. Excessive reduction of serum UA concentrations by ULM might increase VF risk." (VK = vertebral fracture, ULM = uric acid lowering medications)

Iki M, Yura A, Fujita Y, Kouda K, Tachiki T, Tamaki J, Sato Y, Moon JS, Hamada M, Kajita E, Okamoto N, Kurumatani N. Relationships between serum uric acid concentrations, uric acid lowering medications, and vertebral fracture in community-dwelling elderly Japanese men: Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) Cohort Study. Bone. 2020 Oct;139:115519. doi: 10.1016/j.bone.2020.115519. Epub 2020 Jul 2. PMID: 32622874.

"In summary, our results suggest that uric acid has a protective effect on bone metabolism independent of body composition in Chinese postmenopausal females"

Yan DD, Wang J, Hou XH, Bao YQ, Zhang ZL, Hu C, Jia WP. Association of serum uric acid levels with osteoporosis and bone turnover markers in a Chinese population. Acta Pharmacol Sin. 2018 Apr;39(4):626-632. doi: 10.1038/aps.2017.165. Epub 2017 Dec 14. PMID: 29239351; PMCID: PMC5888689.

Sarcopenia is the gradual loss of muscle mass; this muscle loss starts from age 35-40. In men, testosterone levels decline while uric acid levels tend to rise. This loss of testosterone is caused by several factors, one of them being excess inflammatory products. These products include TNF-α, nitric oxide, and IL6. These mediators increase during ageing and reduced by uric acid. Beyond inflammatory products, increased secretion of certain hormones is also associated with bone, muscle brain loss. One of these hormones is parathyroid hormones PTH. PTH generally rises with age and with an excess of phosphorus to calcium intake. High calcium foods like milk contain more calcium than phosphorus, which keeps PTH levels low. Milk is associated with reduced uric acid levels and a reduced incidence of gout. As the PTH level rises, so does uric acid.

Our findings suggested that notwithstanding the associated increased risk of cardiovascular disease, UA might play a protective role in aging-associated decline in muscle strength and cognitive function."

Wu Y, Zhang D, Pang Z, Jiang W, Wang S, Tan Q. Association of serum uric acid level with muscle strength and cognitive function among Chinese aged 50-74 years. Geriatr Gerontol Int. 2013 Jul;13(3):672-7. doi: 10.1111/j.1447-0594.2012.00962.x. Epub 2012 Nov 22. PMID: 23170844.

Our results show that higher UA serum levels are associated with better muscle function in the oldest old and, accordingly, might slow down the progression of sarcopenia."

Molino-Lova R, Sofi F, Pasquini G, Vannetti F, Del Ry S, Vassalle C, Clerici M, Sorbi S, Macchi C. Higher uric acid serum levels are associated with better muscle function in the oldest old: Results from the Mugello Study. Eur J Intern Med. 2017 Jun;41:39-43. doi: 10.1016/j.ejim.2017.03.014. Epub 2017 Mar 23. PMID: 28342714.

"Higher levels of circulating inflammatory markers are significantly associated with lower skeletal muscle strength and muscle mass"

Tuttle CSL, Thang LAN, Maier AB. Markers of inflammation and their association with muscle strength and mass: A systematic review and meta-analysis. Ageing Res Rev. 2020 Dec;64:101185. doi: 10.1016/j.arr.2020.101185. Epub 2020 Sep 26. PMID: 32992047.

"Finally, uric acid reduced the release of the proinflammatory cytokines TNF-α, IL1β, and IL6"

Wang Q, Zhao H, Gao Y, Lu J, Xie D, Yu W, He F, Liu W, Hisatome I, Yamamoto T, Wang W, Cheng J. Uric acid inhibits HMGB1-TLR4-NF-κB signaling to alleviate oxygen-glucose deprivation/reoxygenation injury of microglia. Biochem Biophys Res Commun. 2021 Feb 12;540:22-28. doi: 10.1016/j.bbrc.2020.12.097. Epub 2021 Jan 9. PMID: 33429196.

"In conclusion, the male ALS patients have significantly higher levels of serum uric acid than female patients. There is an inverse correlation between baseline serum uric acid levels and risk of death, prominently in male ALS patients"

Xu LQ, Hu W, Guo QF, Xu GR, Wang N, Zhang QJ. Serum Uric Acid Levels Predict Mortality Risk in Male Amyotrophic Lateral Sclerosis Patients. Front Neurol. 2021 Mar 11;12:602663. doi: 10.3389/fneur.2021.602663. PMID: 33776880; PMCID: PMC7991582.

Hypouricemia

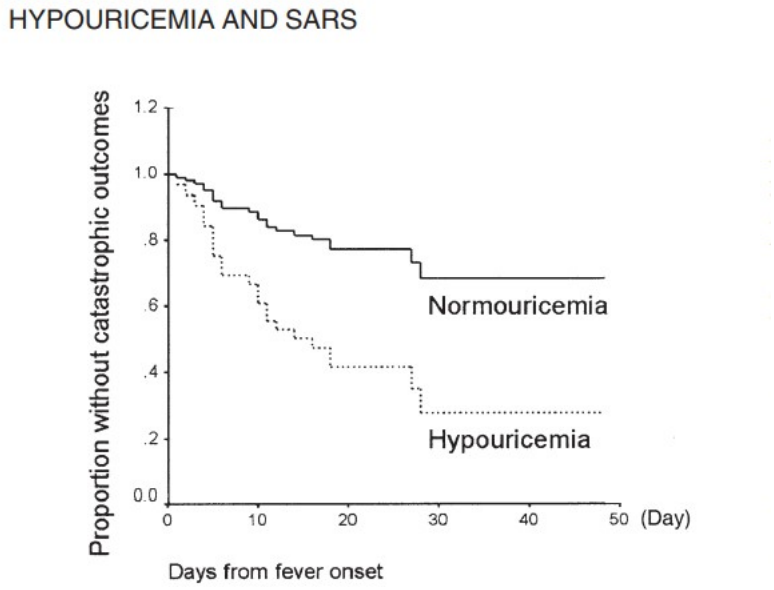
“We found that psychological distress and suicidal ideation severity were associated with lower uric acid serum levels”

Bartoli F, Crocamo C, Bava M, Castagna G, Di Brita C, Riboldi I, Trotta G, Verrengia E, Clerici M, Carrà G. Testing the association of serum uric acid levels with behavioral and clinical characteristics in subjects with major affective disorders: A cross-sectional study. Psychiatry Res. 2018 Nov;269:118-123. doi: 10.1016/j.psychres.2018.08.039. Epub 2018 Aug 15. PMID: 30145291.

“Significant decrease in serum uric acid (P<0.0001) was observed in newly diagnosed major depressive disorder subjects when compared to healthy subjects”

Chaudhari K, Khanzode S, Khanzode S, Dakhale G, Saoji A, Sarode S. Clinical correlation of alteration of endogenous antioxidant-uric acid level in major depressive disorder. Indian J Clin Biochem. 2010 Jan;25(1):77-81. doi: 10.1007/s12291-010-0016-z. Epub 2010 Feb 10. PMID: 23105889; PMCID: PMC3453017.

As is the case with cholesterol, so much attention is given to the possible dangers of high levels, that low levels are neglected. As is the case with cholesterol, infections seem more dangerous when uric acid is lower. A 2005 study found that uric acid in the normal range double the chances of survival compared to low uric acid levels in patients with SARS. Many times low uric acid levels are associated with worse outcomes, compared to normal levels.



Wu VC, Huang JW, Hsueh PR, Yang YF, Tsai HB, Kan WC, Chang HW, Wu KD; SARS Research Group of National Taiwan University College of Medicine and National Taiwan University Hospital. Renal hypouricemia is an ominous sign in patients with severe acute respiratory syndrome. Am J Kidney Dis. 2005 Jan;45(1):88-95. doi: 10.1053/j.ajkd.2004.09.031. PMID: 15696447; PMCID: PMC7115701.

Since early times in uric acid research, little to no attention was given to cutoff levels at the lower ends. A low uric acid level is termed hypouricemia. Many studies found a lower blood plasma of total antioxidant capacity, which uric acid as one of its main components. One of the ways which Selective Serotonin Re-Uptake Inhibitors (SSRI'S) work is by increasing uric acid. Especially women, who already have lower levels, are prone to suffer from depression, anxiety and distress.

"High plasma levels of uric acid were associated with low risk of depression hospitalization and antidepressant medication use."

Wium-Andersen MK, Kobylecki CJ, Afzal S, Nordestgaard BG. Association between the antioxidant uric acid and depression and antidepressant medication use in 96 989 individuals. Acta Psychiatr Scand. 2017 Oct;136(4):424-433. doi: 10.1111/acps.12793. Epub 2017 Aug 28. PMID: 28845530.

"During a comparable follow-up period, 71.4% of the hypouricemic as compared with 38.7% of nonhypouricemic patients died"

Maesaka JK, Cusano AJ, Thies HL, Siegal FP, Dreisbach AW. Hypouricemia in acquired immunodeficiency syndrome. Am J Kidney Dis. 1990 Mar;15(3):252-7. doi: 10.1016/s0272-6386(12)80770-0. PMID: 2305765.

"The generally accepted range of hyperuricemia is: for males, 6.5 to 8 mg. per 100 ml., possibly abnormal; 8 mg. per 100 ml. and above, definitely abnormal; for females, 6 to 7 mg. per 100 ml., possibly abnormal; 7 mg. per 100 ml. and above, definitely abnormal. No range for hypouricemia is given and the cut-off value between normal and below normal is left to the discretion of the clinician"

Lawee D. Uric acid: the clinical application of 1000 unsolicited determinations. Can Med Assoc J. 1969 May 10;100(18):838-41. PMID: 5770706; PMCID: PMC1945194.

"Almost nothing is known about why subjects with low uric acid levels are at an increased risk for mortality. It has been postulated that a low uric acid level could translate into greater oxidative stress, since uric acid is a known antioxidant"

Lee, S. M., Lee, A. L., Winters, T. J., Tam, E., Jaleel, M., Stenvinkel, P., & Johnson, R. J. (2009). Low serum uric acid level is a risk factor for death in incident hemodialysis patients. *American journal of nephrology*, *29*(2), 79–85. https://doi.org/10.1159/000151292

"the risks of low serum uric acid levels and the progression of loss of kidney function might have been underestimated"

Kanda, E., Muneyuki, T., Kanno, Y., Suwa, K., & Nakajima, K. (2015). Uric acid level has a U-shaped association with loss of kidney function in healthy people: a prospective cohort study. *PloS one*, *10*(2), e0118031. https://doi.org/10.1371/journal.pone.0118031

"SUA may be a nutritional marker in HD patients. Contrary to the general population, low but not high SUA is associated with higher all-cause mortality in HD patients, especially in those with low protein intake."

Park C, Obi Y, Streja E, Rhee CM, Catabay CJ, Vaziri ND, Kovesdy CP, Kalantar-Zadeh K. Serum uric acid, protein intake and mortality in hemodialysis patients. Nephrol Dial Transplant. 2017 Oct 1;32(10):1750-1757. doi: 10.1093/ndt/gfw419. PMID: 28064158; PMCID: PMC5837687.

The dangers from low uric acid levels are real. Low uric acid acids may manifest in depression, heart disease and ALS. Many times scientist equates low uric acid levels with malnutrition, favoring malnutrition as a cause instead of uric acid.

“In addition, the plasma levels of uric acid in patient groups were significantly and inversely correlated with psychosis. There was a trend for lower uric acid levels in relapsed patients relative to clinically stable patients”

Psychiatry Res. 1998 Jul 27;80(1):29-39. Reduced level of plasma antioxidant uric acid in schizophrenia. Yao JK, Reddy R, van Kammen DP

“The uric acid levels measured in serum of patients with a prostate cancer diagnosis were reduced compared to the control group and inflammatory markers were found to be increased. Low serum uric acid levels and increased inflammatory markers were determined as risk factors for prostate cancer.”

Benli, Erdal et al. “Comparison of serum uric acid levels between prostate cancer patients and a control group.” *Central European journal of urology* vol. 71,2 (2018): 242-247. doi:10.5173/ceju.2018.1619

“In conclusion, the male ALS patients have significantly higher levels of serum uric acid than female patients. There is an inverse correlation between baseline serum uric acid levels and risk of death, prominently in male ALS patients”

Xu L-Q, Hu W, Guo Q-F, Xu G-R, Wang N and Zhang Q-J (2021) Serum Uric Acid Levels Predict Mortality Risk in Male Amyotrophic Lateral Sclerosis Patients. *Front. Neurol.* 12:602663. doi: 10.3389/fneur.2021.602663

UA levels were positively associated with muscle mass and strength, but not with functional capacity, in KTPs.

Floriano JP, Nahas PC, de Branco FMS, et al. Serum Uric Acid Is Positively Associated with Muscle Mass and Strength, but Not with Functional Capacity, in Kidney Transplant Patients. *Nutrients*. 2020;12(8):2390. Published 2020 Aug 10. doi:10.3390/nu12082390

These results suggest that serum UA may have a protective role in aging-associated decline in muscle strength in community-dwelling elderly women

Kawamoto R, Ninomiya D, Kasai Y, Kusunoki T, Ohtsuka N, Kumagi T, Abe M. Serum Uric Acid Is Positively Associated with Handgrip Strength among Japanese Community-Dwelling Elderly Women. PLoS One. 2016 Apr 14;11(4):e0151044. doi: 10.1371/journal.pone.0151044. PMID: 27078883; PMCID: PMC4831672.

Uric Acid Treatment

Now that we understand that uric acid is mostly a consequence of inflammation and not a cause of it, uric acid supplementation makes more sense. Uric acid supplementation studies with animals are impressive, but these results have to taken with a grain of salt. As most animals have very low levels of uric acid, giving large amount of this might have benefits that are not transferable to humans. Studies with rats show that uric acid treatment increased survival and uric acid is suggested as treatment for neurological diseases.

Going through the literature, there is a case to make to increase uric acid levels. The best way to increase uric acid would be fruits, as fructose is associated with an increase in uric acid. A future approach could be to have an uric acid treatment, as those are currently popular with glutathione. As some research shows uric acid infusion lasts several hours, it might be interesting for athletes as a pre-game feature. Studies with healthy people indicate that intake up to 1000 mg of uric acid reports no ill-effects.

Studies in human with uric acid are rare but promising. One of the key features and benefits of uric acid is the suppression of peroxynitrites or their derivatives in the mitochondria. Nitric oxide can react with superoxide forming peroxynitrites. These peroxynitrites can make amino acids like tyrosine less functional and inhibit mitochondrial workings. Of the different subunits which contain peroxynitrites, uric acid scavenges these radicals and brings the mitochondria back to normality.

“Our study shows that UA normalized activity of complexes I and V and improved activity of complexes II and III.. A striking finding in our study was that treatment with UA resulted in a nearly complete resolution of fatty liver in these animals..Treatment of these animals with uric acid, ... decreased tyrosine nitrated proteins, improved the activity of MRC complexes, and led to a marked regression of hepatic steatosis and inflammation"

García-Ruiz I, Rodríguez-Juan C, Díaz-Sanjuan T, del Hoyo P, Colina F, Muñoz-Yagüe T, Solís-Herruzo JA. Uric acid and anti-TNF antibody improve mitochondrial dysfunction in ob/ob mice. Hepatology. 2006 Sep;44(3):581-91. doi: 10.1002/hep.21313. PMID: 16941682.

“Each of these conditions is associated with an increased serum uric acid concentration, possibly conferring protection against persistent exposure to potentially damaging vascular oxidants, characteristically found in these conditions”

“We did not observe any adverse effects after administration of uric acid, 1,000 mg, in this study and we believe that the consequent short term elevation of serum uric acid concentration poses a very low risk”

“Uric acid can safely be administered to increase serum concentrations in man, and subsequently enhance antioxidant activity of the extracellular compartment”

Waring WS, Maxwell S. Diagnosis of molybdenum cofactor deficiency. Lancet. 1999 Feb 20;353(9153):675-6. doi: 10.1016/S0140-6736(05)75474-X. PMID: 10030364.

“In this sample of cognitively healthy, community-dwelling adults, we found that higher SUA levels at baseline were associated with attenuated declines in attention and visuospatial abilities in men”

Kueider AM, An Y, Tanaka T, Kitner-Triolo MH, Studenski S, Ferrucci L, Thambisetty M. Sex-Dependent Associations of Serum Uric Acid with Brain Function During Aging. J Alzheimers Dis. 2017;60(2):699-706. doi: 10.3233/JAD-170287. PMID: 28922153; PMCID: PMC6112110

“We conclude that raised UA levels are associated with higher BMD at all skeletal sites and UA may have a protective role in bone metabolism owing to its antioxidant effect”

Kaushal, N., Vohora, D., Jalali, R. K., & Jha, S. (2018). Raised serum uric acid is associated with higher bone mineral density in a cross-sectional study of a healthy Indian population. *Therapeutics and clinical risk management*, *14*, 75–82. https://doi.org/10.2147/TCRM.S147696

“Here, we found that lower serum uric acid levels are linked to cognitive dysfunction. In a Mexican population, higher levels of uric acid are associated with a decreased risk of dementia.”

Méndez-Hernández E, Salas-Pacheco J, Ruano-Calderón L, Téllez-Valencia A, Cisneros-Martínez J, Barraza-Salas M, Arias-Carrión O. Lower uric Acid linked with cognitive dysfunction in the elderly. CNS Neurol Disord Drug Targets. 2015;14(5):564-6. doi: 10.2174/1871527314666150430161659. PMID: 25925000.

“Decreased serum UA levels were associated with suicide risk in MDD patients. Purinergic system dysfunction may be involved in the neurobiological basis of suicide risk in these patients.”

Chen JX, Feng JH, Zhang LG, Liu Y, Yang FD, Wang SL, Tan YL, Su YA. Association of serum uric acid levels with suicide risk in female patients with major depressive disorder: a comparative cross-sectional study. BMC Psychiatry. 2020 Sep 29;20(1):477. doi: 10.1186/s12888-020-02891-8. PMID: 32993584; PMCID: PMC7526231.

“This study provided novel evidence that SUA-mortality association differed by sex. We demonstrated that a lower SUA was an independent risk factor for all-cause mortality in men with normal kidney function”

Kang E, Hwang SS, Kim DK, Oh KH, Joo KW, Kim YS, Lee H. Sex-specific Relationship of Serum Uric Acid with All-cause Mortality in Adults with Normal Kidney Function: An Observational Study. J Rheumatol. 2017 Mar;44(3):380-387. doi: 10.3899/jrheum.160792. Epub 2017 Jan 15. PMID: 28089980.

“In the ischemic rat brain, the administration of uric acid results in neuroprotection and improved behavioral outcome. The severity of neurological impairment and the volume of infarction in patients with stroke have been found inversely related to the concentration of uric acid. In healthy volunteers, uric acid has been administered without untoward effects to show a conspicuous reduction of oxidative stress. We hypothesize that the administration of uric acid could be beneficial and cost effective in patients sustaining acute oxidative stress, such as those with acute ischemic stroke. Uric acid could also extend to more than 3 h the therapeutic window of rt-PA after stroke and it could limit the appearance of neurobehavioral changes after cardiopulmonary bypass.”

Chamorro A, Planas AM, Muner DS, Deulofeu R. Uric acid administration for neuroprotection in patients with acute brain ischemia. Med Hypotheses. 2004;62(2):173-6. doi: 10.1016/S0306-9877(03)00324-4. PMID: 14962621.

Serum uric acid levels could be used as a biomarker for monitoring disease activity in MS. Therapeutic strategies aimed at raising serum uric acid levels may have a glial/neuroprotective effect on MS patients."

Koch M, De Keyser J. Uric acid in multiple sclerosis. Neurol Res. 2006 Apr;28(3):316-9. doi: 10.1179/016164106X98215. PMID: 16687059.

Can We Substitute Uric Acid?

In the beginning of this booklet, we noticed that caffeine is in the same class of molecules called purines. Caffeine containing beverages like coffee are known for many of the same benefits as uric acid. These benefits include protecting against brain disorders and depression.

Several added benefits of caffeine containing beverages like coffee are suppression of xanthine oxidase and ability to stop the absorption of iron into the body. These ways are likely major reasons why uric acid is lowered by coffee, and why uric acid can stay within normal levels. Limiting iron intake stops inflammation. Milk is associated with a lower incidence of gout and lower uric acid levels. Milk also blocks iron and the calcium in milk can keep parathyroid hormone (PTH) within the normal range. PTH is an inflammatory hormone and is positively correlated with uric acid. As PTH goes up, uric acid rises. Magnesium levels are inversely correlated with uric acid. As magnesium intake goes up, uric acid levels tend to go down.

The increase in brain volume roughly coincides with the initiation of cooking our food. It is interesting that roasting coffee beans (in this case caffeic acid) increases their ability to inhibit xanthine oxidase. It is likely that increasing magnesium and calcium reduce uric acid.

“The high-temperature treatment of caffeic acid by a model reaction for the processing of foods by roasting enhanced its xanthine oxidase (XO) inhibitory activity”

Masuda T, Fukuyama Y, Doi S, Masuda A, Kurosawa S, Fujii S. Effects of Temperature on the Composition and Xanthine Oxidase Inhibitory Activities of Caffeic Acid Roasting Products. J Agric Food Chem. 2019 Aug 14;67(32):8977-8985. doi: 10.1021/acs.jafc.9b03633. Epub 2019 Aug 2. PMID: 31334649.

“Coffee drinking may be associated with decreased systemic oxidative DNA damage through decreasing body iron storage in women.”

Hori A, Kasai H, Kawai K, Nanri A, Sato M, Ohta M, Mizoue T. Coffee intake is associated with lower levels of oxidative DNA damage and decreasing body iron storage in healthy women. Nutr Cancer. 2014;66(6):964-9. doi: 10.1080/01635581.2014.932398. Epub 2014 Jul 25. PMID: 25062326.

“Increased serum PTH level was significantly associated with increased serum uric acid level ... Increased PTH level was also significantly associated with the condition of hyperuricemia in the study population”

Chin KY, Nirwana SI, Ngah WZ. Significant association between parathyroid hormone and uric acid level in men. Clin Interv Aging. 2015 Aug 21;10:1377-80. doi: 10.2147/CIA.S90233. PMID: 26346636; PMCID: PMC4552259.

“Our results suggest body iron storage is a strong determinant of levels of systemic oxidative DNA damage in a healthy population.”

Hori A, Mizoue T, Kasai H, Kawai K, Matsushita Y, Nanri A, Sato M, Ohta M. Body iron store as a predictor of oxidative DNA damage in healthy men and women. Cancer Sci. 2010 Feb;101(2):517-22. doi: 10.1111/j.1349-7006.2009.01394.x. Epub 2009 Oct 10. PMID: 19895603.

“The beneficial effects of coffee now warrant the effect of lowering level of uric acid and sugar hence improving insulin sensitivity. Further, the antioxidant activity decreases the oxidative damage thus improving the quality of health of people thus coffee can act as a therapeutic intervention among the people with higher risk factors for diabetes and its associated complications”

Bhaktha, Geetha & Shantaram, Manjula & Nayak, Shivananda. (2016). Beneficial effects of coffee and maintenance of uric acid levels. International Journal of Pharmacy and Pharmaceutical Sciences. 8. 393 to 395.

“These findings from a nationally representative sample of US adults suggest that coffee consumption is associated with lower serum uric acid level and hyperuricemia frequency, but tea consumption is not. The inverse association with coffee appears to be via components of coffee other than caffeine”

Choi HK, Curhan G. Coffee, tea, and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. Arthritis Rheum. 2007 Jun 15;57(5):816-21. doi: 10.1002/art.22762. PMID: 17530681.

“Furthermore, there is still no consensus if UA is a protective or a risk factor, however, it seems that the quantity and the duration of the concentration of the uric acid in the blood is essential for this answer. Acute elevation seems to be a protective factor, whereas chronic elevation a risk factor”

de Oliveira, Erick Prado, and Roberto Carlos Burini. “High plasma uric acid concentration: causes and consequences.” *Diabetology & metabolic syndrome* vol. 4 12. 4 Apr. 2012, doi:10.1186/1758-5996-4-12

For more information visit www.fishybusiness.site