SZCZEPAŃSKI, Michał, DZIESZKO, Natalia, BOROWSKI, Maciej, KALINOWSKA, Weronika, KULASZA, Paulina Sara, FRANCUZIAK, Anna Ewelina, DEMBICKI, Piotr Mikołaj, KOZŁOWSKA, Kinga, KSIĄŻEK, Tomasz Karol and SZELIGA, Aleksandra. Is Urate-lowering therapy a prevention of first gout episode? Quality in Sport. 2025;43:61492. eISSN 2450-3118.
https://doi.org/10.12775/QS.2025.43.61492
https://apcz.umk.pl/QS/article/view/61492

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 26.05.2025. Revised: 05.07.2025. Accepted: 05.07.2025. Published: 10.07.2025.

Is Urate-lowering therapy a prevention of first gout episode?

1. Michał Szczepański [MS]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0002-4828-6709
michalszczepanski99@gmail.com

2. Natalia Dzieszko [ND]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0008-8743-6590
1nataliadzieszko9@gmail.com

3. Maciej Borowski [MB]
Univeristy Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland
https://orcid.org/0009-0006-4185-2199
mborowski800@gmail.com

4. Weronika Kalinowska [WK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0005-4630-467X
wkalinowska999@gmail.com

5. Paulina Sara Kulasza [PSK]
Jędrzej Śniadecki Regional Hospital in Białystok, Marii Skłodowskiej-Curie 26 Street, 15-278 Białystok, Poland
https://orcid.org/0009-0003-5829-6721
pkulasza@onet.pl

6. Anna Ewelina Francuziak [AEF]
University Hospital in Krakow, Kopernika 36 street, 31-501 Krakow, Poland
https://orcid.org/0009-0005-9810-7758
anna.fr17@wp.pl

7. Piotr Mikołaj Dembicki [PMD]
Ludwik Rydygier Memorial Specialized Hospital, Osiedle Złotej Jesieni 1 street, 31-820 Krakow, Poland
https://orcid.org/0009-0005-0709-9220
piotr.dembickizmc@gmail.com

8. Kinga Kozłowska [KK]
Provincial Hospital of Podkarpackie John Paul II in Krosno, Korczyńska 57 street, 38-400 Krosno, Poland
https://orcid.org/0009-0008-6541-207X
Kinga7839@gmail.com

9. Tomasz Karol Książek [TKK]
Univeristy Clinical Hospital of Bialystok, Marii Skłodowskiej-Curie 24A street, 15-276 Białystok, Poland
https://orcid.org/0009-0000-9852-1434
ksitomasz@gmail.com

10. Aleksandra Szeliga [AS]
Medical Univeristy of Białystok, Jana Kliniśkiego 1 street, 15-089 Białystok, Poland
https://orcid.org/0009-0006-1832-5569
Aleksandra.sze97@gmail.com

Abstract

The growing problem of gout is beginning to raise questions about how we can effectively prevent this disease. This work examines the effect of urate-lowering therapy on preventing the onset of a first episode of gout—an effect that is not entirely clear, despite the fact that such therapy is an essential tool for controlling gout flares. A growing database allows us to analyze the impact of hyperuricemia, which has so far been presumed to be a major contributor to the development of gout, and assess its actual impact on the development of the disease.

Material and methods

Data bases such as Pubmed and Google Scholar were used for research with the key words: urate-lowering therapy, gout, symptomless hyperuricemia, serum uric acid

Conclusions

While hyperuricemia is a proven risk factor for the development of gout, lowering serum uric acid does not necessarily reduce the incidence of a first gout episode. This may be due to the different pathways through which uric acid and monosodium urate (MSU) crystals activate the inflammatory process. Additionally, risk factors such as overweight, diet, and alcohol consumption—which contribute to elevated serum uric acid levels—are also significant. This raises the observation that the factors leading to hyperuricemia may be more important than hyperuricemia itself. Nevertheless, the introduction of urate-lowering therapy (ULT) has many benefits, such as reducing the risk of mortality and comorbidities, and therefore should not be dismissed in asymptomatic hyperuricemic patients.

Keyword:
urate-lowering therapy, gout, symptomless hyperuricemia, serum uric acid

1. Introduction

• Epidemiology

Gout is the most prevalent type of inflammatory arthritis, affecting 41 million adults globally[1]. Multiple studies indicate that its incidence has increased in recent decades[2]. It disproportionately affects men, with a male-to-female ratio of 4:1, which decreases to 3:1 after menopause[3]. Despite the rising incidence of acute gout, effective pharmaceutical options for managing hyperuricemia have been introduced, making classical gout-specific morphological degenerations increasingly rare[4,5].

• Hyperuricemia

Hyperuricemia is state when serum uric acid (SUA) concentration exceeds 7 mg/dL (420 μmol/L)[6]. This disorder is caused by uric acid imbalance in production and disposal, leading to growth of serum urates level[7]. Genetic factors also play a significant role in determining SUA levels, with 43 genes currently identified as regulators of uric acid concentration[8].

Numerous studies have shown that hyperuricemia is a risk factor for developing hypertension, metabolic syndrome, insulin resistance, dyslipidemia, type 2 diabetes mellitus, chronic kidney disease, and cardiovascular disorders[9,10,11]. It can be explained by fact that high concentration of uric acid manifest pro-inflammatory effects, including activation of the renin–angiotensin system, increasing oxidative stress, and promoting insulin resistance[12,13,14]. In vivo study showed that leukocytes are forming aggregates on uric acid crystals, confirming the pro-inflammatory properties of this compound[15,16].

However, the role of uric acid in the human body is not solely negative. It also has antioxidant properties that help combat free radicals[17]. In this way, uric acid may inhibit cell death, support nerve protection, and enhance nitric oxide (NO)-induced vasodilation[7,18]. Furthermore, it exhibits protective effects against various neurodegenerative disorders, suggesting that it may play a beneficial role in neuronal growth and activity[19].

2. Pathophisiology

• Uric Acid Metabolism

Purine containing adenine and guanine are crucial for the creation of DNA and RNA Purines are essential components for proper physiological function in humans. The connection between purines and gout arises from the fact that purine metabolism results in the generation of urate.

Adenosine is metabolized into inosine by adenosine deaminase, that is metabolized by purine nucleoside phosphorylase (PNP) into hypoxanthine. Xanthine oxidase metabolizes hypoxanthine into xanthine, and further into uric acid. Guanine deaminase metabolizes guanine into xanthine, after which xanthine oxidase metabolizes it into uric acid. [20]

In some animal species, uric acid is converted by uricase to the well-water-soluble allantoin, but humans and some primate species lack this enzyme, leading to the need for active urate excretion, resulting in higher serum level of urate[19].

• Crystal Formation

Gout occurs due to the formation of monosodium urate (MSU) crystals, which result from hyperuricemia exceeding the solubility threshold of uric acid in bodily fluids. The development of polarized light microscopy in the mid-20th century enabled the detection of MSU crystals in the joint fluid of patients, establishing hyperuricemia and urate crystals as the underlying cause of the disease[21].

MSU crystals form in favorable areas such as joint cartilage synovial bursae, and tendons[22,23]. Crystal formation may be influenced by the presence of solutions containing hyaluronate, sodium (Na^+) ions, and calcium (Ca^{2+}) ions. The greater water solubility of the hyaluronate–calcium–urate complex, compared to free urate ions, may explain why only some patients with hyperuricemia develop gout.[24]

• Role of SUA and MSU in inflammation

Hyperuricemia may trigger inflammation by promoting the production of inflammatory agents such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP)[25]. Some studies suggest that the NLRP3 inflammasome—a component of the nucleotide-binding domain and leucine-rich repeat (NLR) protein family—

is essential in the development of inflammatory disorders[26,27]. Although both SUA and MSU crystals can provoke immune responses, they do so through distinct pathways involving separate priming and activation mechanisms[28]. This divergence may explain the increased inflammatory response observed when gout coexists with hyperuricemia. In fact, patients with both conditions show a higher risk of mortality compared to those with either condition alone, supporting the hypothesis of a compounded inflammatory response[29].

Additionally, individuals with asymptomatic hyperuricemia often exhibit reduced inflammatory activity, including fewer $NKG2D^{+}$ natural killer (NK) cells, which are key receptors in stimulating cytotoxic responses. It has been hypothesized that the paradoxical relationship between SUA and inflammation may arise because SUA can neutralize reactive oxygen species (ROS) generated during inflammation, thereby protecting tissues from damage.

It can be proposed that while hyperuricemia might encourage the creation of SUA crystals and enhance immune responses contributing to gout flares, it follows opposing inflammatory pathways compared to those involving MSU crystals. Hyperuricemia might not be the sole factor influencing a gout flare particularly regarding inflammation, and it can occur even in some patients without crystal formation. Certainly, the variation in inflammation pathways might provide insight into the significance of addressing other inflammation factors besides hyperuricemia during a gout attack.[30,31]

3. Strategies for lowering SUA

- **Lifestyle modifications**

Diets

The three most commonly recommended diets for lowering uric acid levels and managing gout exacerbations are the DASH diet, the Mediterranean diet, and the low-purine diet. Each is briefly described below.

DASH

The DASH diet was originally developed to help manage high blood pressure. It is a plant-centered eating pattern rich in fruits, vegetables, and nuts, and includes low-fat or fat-free dairy products, lean meats, fish, poultry, mostly whole grains, and heart-healthy fats. The diet recommends limiting red meat, desserts, sugary beverages, saturated fats, total fat, and cholesterol. Although studies have shown that the DASH diet has a statistically significant effect on lowering serum uric acid levels, the reduction is generally too small for it to be considered an optimal treatment for hyperuricemia[32,33].

Mediterranean Diet

The Mediterranean diet emphasizes the consumption of plant-based proteins, whole grains, fish, and monounsaturated fats (such as olive oil), along with moderate wine consumption, while minimizing red meat and refined grains[34].

tudies have not demonstrated a significant effect of the Mediterranean diet on lowering uric acid levels in hyperuricemic individuals after two years of use[35]. However, adherence to the

Mediterranean diet has been associated with a reduced risk of developing hyperuricemia[36], leaving its impact on controlling gout uncertain.

Low Purine Diet

A low-purine diet is the primary dietary recommendation for managing gout exacerbations. It is based on the idea that avoiding purine-rich foods leads to lower concentrations of uric acid, the end product of purine metabolism. This diet typically involves avoiding foods such as shellfish, organ meats, alcoholic beverages, and canned fish like sardines. Notably, studies have shown an increased risk of gout with higher intake of meat and seafood, while purine-rich vegetables do not appear to increase this risk.

It is believed that a low-purine diet can reduce mean serum urate levels by approximately 1 mg/dL. However, even with a strict diet, urate-lowering treatment is still required to reach target uric acid levels[37,38]. Short-term exposure to purines from animal sources has been shown to increase the risk of a gout attack fivefold. However, there are no studies examining the long-term effects of a purine-rich diet on gout flares[39].

Weight Loss

Obesity is a growing problem worldwide, and in the context of our subcjet, it is all the more important because multiple studies show correlations between BMI and the risk of gout and hyperuricemia.[40,41] Weight loss in the example of patients after bariatric surgery shows a significant reduction of risk developing gout and decreasing serum uric acid levels compared to patients who have not undergone such surgery.[42,43,44,45]

Therefore, losing weight seems to positively influence the prevention of new gout cases, lower serum urate levels, and lessen the occurrence of flare-ups. These results align with the earlier studies that assessed the contributions of diet and genetics, where weight was consistently recognized as a significant factor influencing serum urate levels.

Alcohol Cessation

Alcohol consumption has a significant effect on serum uric acid levels, showing a correlation between increased beer and liquor consumption on increased serum uric acid levels, but showing no such correlation for wine.[46] In gout-free subjects, beer consumption raised the risk of a first gout episode more than liquor consumption, showing no increase in risk for moderate wine consumption.[47] Serum uric acid levels in heavy drinking patients (30 units or more per week) were on average 1.6 mg/dL lower than in abstainers, also alcohol consumption reduced the effectiveness of serum uric acid-lowering therapy resulting in more gout flares.[48] Resulting in the fact that current guidelines indicate to limit consumption of all types of alcohol in gout patients.[49]

- ## Pharmacological Interventions

Urate-lowering therapy is one of the main ways to control gout flares. However, the beneficial effect of the action of these drugs is multisite. Studies prove a reduction in the risk of death in post-MI patients using ULT[50], as well as improved control of chronic kidney

disease, but no evidence has been presented to reduce the incidence of AKI.[51] Below will be presented the basic types of urate-lowering therapies.

First Line Options

Allopurinol

This drug is a xanthine oxidase inhibitor that acts by stopping the metabolic pathway of uric acid resulting in a reduction of its concentration in the bloodstream. The starting dose is usually 100mg daily.

Its effects are not limited to the treatment of gout. Study shows allopurinol exhibits oxidative stress-reducing abilities and deacreases the morbidity and mortality among congestive heart failure patients, potentially by enhancing mechanoenergetic uncoupling, leading to improvement of contractility of hearth left ventricle and ejection fraction.[52,53,54] Another research shows a possible role for it in improving endothelial dysfunction, but caveats that this requires further research to confirm causality.[55]

As a genereally safe drug, it is not free of side effects. The most common side effects are those involving the skin. Hypersensitivity reactions can be life-threatening, especially in patients with renal impairment.[56] However, certain steps can be taken to reduce the risk of adverse reactions, as in the case of allopurinol hypersensitivity syndrome(AHS), testing for the presence of the HLA-B*58:01 gene is recommended in some populations, because its presence increases the risk of AHS 100 times.[57]

Febuxostat

Similar to allopurinol, febuxostat is a xanthine oxidase inhibitor, but they differ in the way they are metabolized-febuxostat is metabolized by the liver and not by the kidneys like allopurinol, so in its case there is no need to change the dosage if renal failure coexists.[58,59] Studies show that with a dosage range of 40-80mg/d febuxostat is better at lowering concentrations of serum uric acid than allopurinol (200-300mg/d), but is less efficient in preventing gout flares.[60] Additional actions of febuxostat go as far as such surprising abilities as antibacterial, inhibiting the growth of Mycobacterium tuberculosis more effectively than allopurinol or xanthine oxidase specific inhibitor- topiroxostat.[61] The side effects of febuxostat center around liver function, most commonly causing elevations in liver enzymes.[62] There are many papers comparing the safety of febuxostat and allopurinol, some of which point to the benefit of febuxostat, but outline possibility of gout flare when using it.[60,62,63,64,65]

Second Line Options

Probenecid

Probenecid belongs to the group of uricosuric drugs, that is, it increases the secretion of uric acid with urine. It acts by inhibiting the reabsorption of uric acid in renal tubules. Originally, it was intended to be used to increase penicillins concentration in bloodstream.[66] Another of its uses can be more effective against venereal diseases, some viral infections and it also shows antibacterial activity.[67,68,69,70] Side effects of probenecid are usually not life-threatening, the most common are headache, rash, and due to its mechanism of action sometimes patients develop kidney stones due to increased uric acid in the urine.[71,72]

Pegloticase

It is a recombinant uricase whose action is to catalyze the reaction of converting uric acid to the well-water-soluble allantoin, which is excreted in the urine. As an intravenous drug, it should be administered at a dose of 8mg once every two weeks. Since it can trigger a gout attack, it is recommended that prophylaxis in the form of colchicine or NSAIDs be implemented prior to its use.[73]

4. SUA Reduction in Gout Prevention

Hyperuricemia is considered a risk factor for developing gout, however not all patients with elevated uric acid levels manifest symptoms of gout, and some patients suffering from it have serum uric acid levels within the normal range, for example survey from years 2006-2007 showed that only 21.2% of man and 21.6% of woman with gout had coexisting hyperuricemia.[74,75] There is also a lack of evidence for preventing the first gout episode with allopurinol, which also raises questions about hyperuricemia as the only factor affecting the development of gout.[76] Some works cite different pathways of activation of the inflammatory process in the presence of MSU crystals as a possible cause. Which, combined with both the antioxidant and pro-inflammatory abilities of uric acid, might explain asymptomatic hyperuricemia without developed gout and gout flares in normuricemic patients.[77]

Nevertheless, elevated serum uric acid levels remain an important risk factor for the development of gout, gout flares, and its role in the pathogenesis of other diseases has been confirmed by many studies.[10,12,13,16,78,79] And the introduction of therapy that lowers serum uric acid levels has positive effects in pulmonary arterial hypertension or improves renal function in chronic kidney disease.[80,81]

Author contribution

Conceptualization: Michał Szczepański, Natalia Dzieszko, Maciej Borowski
Methodology: Michał Szczepański, Natalia Dzieszko, Weronika Kalinowska
Investigation: Michał Szczepański, Natalia Dzieszko, Paulina Sara Kulasza
Software: Anna Ewelina Francuziak, Piotr Mikołaj Dembicki, Weronika Kalinowska, Paulina Sara Kulasza
Check: Piotr Mikołaj Dembicki, Weronika Kalinowska

Data curation: Weronika Kalinowska, Anna Ewelina Francuziak
Visualization: Piotr Mikołaj Dembicki, Anna Ewelina Francuziak
Project administration: Michał Szczepański
Writing -rough preparation: Michał Szczepański, Natalia Dzieszko
Formal analysis: Anna Ewelina Francuziak, Piotr Mikołaj Dembicki, Kinga Kozłowska
Writing –review and editing: Anna Ewelina Francuziak, Kinga Kozłowska
Resources: Maciej Borowski, Aleksandra Szeliga, Tomasz Karol Książek
Supervision: Maciej Borowski, Aleksandra Szeliga, Tomasz Karol Książek

All authors have read and agreed with the published version of the manuscript.

Funding statement:
The article did not receive funding.

Statement of institutional review board:
Not applicable.

Statement of informated consent:
Not applicable.

Statement of data availability:
Not applicable.

Conflict of interest statement:
The authors declare not conflict of interest.

Declaration of the use of generative AI and AI-assisted technologies in the writing process.

In preparing this work, the author(s) used Open AI Chat Generative Pre-trained Transformer for the purpose of correcting spelling mistakes, punctuation mistakes, grammatical errors and stylistic errors. After using this tool/service, the author(s) have reviewed and edited the content as needed and accept full responsibility for the substantive content of the publication.

References:

1. Danve A, Sehra ST, Neogi T. Role of diet in hyperuricemia and gout. Best Practice and Research: Clinical Rheumatology 35 2021.
2. Roddy E, Doherty M. Epidemiology of gout. Arthritis Research and Therapy 12 2010.
3. Ankli B. Gicht – Neues zur epidemiologie. Therapeutische Umschau 73 2016 125–129.
4. Mertz DP. Changes in the epidemiology, symptomatology and prognosis of gout. Versicherungsmedizin / herausgegeben von Verband der Lebensversicherungs-Unternehmen e.V. und Verband der Privaten Krankenversicherung e.V 44 1992 10–13.

5. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nature Reviews Rheumatology 16 2020 380–390.
6. Szczeklik A. Interna Szczeklika. Medycyna Praktyczna, 2024.
7. Du L, Zong Y, Li H et al. Hyperuricemia and its related diseases: mechanisms and advances in therapy. Signal Transduction and Targeted Therapy 9 2024.
8. Boocock J, Leask M, Okada Y et al. Genomic dissection of 43 serum urate-associated loci provides multiple insights into molecular mechanisms of urate control. Hum Mol Genet 2020; 29: 923–943.
9. Kuwabara M, Niwa K, Hisatome I et al. Asymptomatic Hyperuricemia Without Comorbidities Predicts Cardiometabolic Diseases Five-Year Japanese Cohort Study. Hypertension 2017; 69: 1036–1044.
10. Liu YF, Han L, Geng YH, Wang HH, Yan JH, Tu SH. Nonlinearity association between hyperuricemia and all-cause mortality in patients with chronic kidney disease. Sci Rep 2024; 14.
11. Nadeem ZA, Nashwan AJ. Comment on: 'Gout/hyperuricemia reduces the risk of Alzheimer's disease: A meta-analysis based on latest evidence'. Brain and Behavior 14 2024.
12. Zhou X, Matavelli L, Frohlich ED. Uric acid: Its relationship to renal hemodynamics and the renal renin-angiotensin system. Curr Hypertens Rep 2006; 8: 120–124.
13. Park JH, Jin YM, Hwang S, Cho DH, Kang DH, Jo I. Uric acid attenuates nitric oxide production by decreasing the interaction between endothelial nitric oxide synthase and calmodulin in human umbilical vein endothelial cells: A mechanism for uric acid-induced cardiovascular disease development. Nitric Oxide 2013; 32: 36–42.
14. Wan X, Xu C, Lin Y et al. Uric acid regulates hepatic steatosis and insulin resistance through the NLRP3 inflammasome-dependent mechanism. J Hepatol 2016; 64: 925–932.
15. Lu Z, Lu F, Zhang R, Guo S. Interaction between anemia and hyperuricemia in the risk of all-cause mortality in patients with chronic kidney disease. Front Endocrinol (Lausanne) 2024; 15.
16. Crane JK, Mongiardo KM. Pro-inflammatory effects of uric acid in the gastrointestinal tract. Immunol Invest 2014; 43: 255–266.
17. Gherghina ME, Peride I, Tiglis M, Neagu TP, Niculae A, Checherita IA. Uric Acid and Oxidative Stress—Relationship with Cardiovascular, Metabolic, and Renal Impairment. International Journal of Molecular Sciences 23 2022.
18. Weaver VM, Schwartz BS, Jaar BG et al. Associations of uric acid with polymorphisms in the δ-aminolevulinic acid dehydratase, vitamin D receptor, and nitric oxide synthase genes in Korean lead workers. Environ Health Perspect 2005; 113: 1509–1515.
19. Álvarez-Lario B, Macarrón-Vicente J. Uric acid and evolution. Rheumatology 49 2010 2010–2015.
20. Brzozowski T. Konturek : Fizjologia człowieka. 2019.
21. MCCARTY DJ, HOLLANDER JL. Identification of urate crystals in gouty synovial fluid. Ann Intern Med 1961; 54: 452–460.
22. Chhana A, Pool B, Wei Y et al. Human Cartilage Homogenates Influence the Crystallization of Monosodium Urate and Inflammatory Response to Monosodium Urate Crystals: A Potential Link Between Osteoarthritis and Gout. Arthritis and Rheumatology 2019; 71: 2090–2099.
23. Dehlin M, Jacobsson L, Roddy E. Global epidemiology of gout: prevalence, incidence, treatment patterns and risk factors. Nature Reviews Rheumatology 16 2020 380–390.

24. Chih MH, Lee HL, Lee T. The culprit of gout: triggering factors and formation of monosodium urate monohydrate. CrystEngComm 2015; 18: 290–297.
25. Kirilmaz B, Asgun F, Alioglu E et al. High inflammatory activity related to the number of metabolic syndrome components. J Clin Hypertens 2010; 12: 136–144.
26. Riaz M, Kury LT Al, Atzaz N et al. Carvacrol Alleviates Hyperuricemia-Induced Oxidative Stress and Inflammation by Modulating the NLRP3/NF-κB Pathwayt. Drug Des Devel Ther 2022; 16: 1159–1170.
27. Kim SM, Lee SH, Kim YG et al. Hyperuricemia-induced NLRP3 activation of macrophages contributes to the progression of diabetic nephropathy. Am J Physiol Renal Physiol 2015; 308: F993–F1003.
28. Alberts BM, Bruce C, Basnayake K, Ghezzi P, Davies KA, Mullen LM. Secretion of IL-1β from monocytes in gout is redox independent. Front Immunol 2019; 10.
29. Li S, Cui L, Cheng J et al. Repeated measurements of serum urate and mortality: A prospective cohort study of 152,358 individuals over 8 years of follow-up. Arthritis Res Ther 2020; 22.
30. Zhang Q, Gong H, Lin C et al. The prevalence of gout and hyperuricemia in middle-aged and elderly people in Tibet Autonomous Region, China: A preliminary study. Medicine (United States) 2020; 99.
31. Cabău G, Crișan TO, Klück V, Popp RA, Joosten LAB. Urate-induced immune programming: Consequences for gouty arthritis and hyperuricemia. Immunological Reviews 294 2020 92–105.
32. Juraschek SP, Yokose C, McCormick N, Miller ER, Appel LJ, Choi HK. Effects of Dietary Patterns on Serum Urate: Results From a Randomized Trial of the Effects of Diet on Hypertension. Arthritis and Rheumatology 2021; 73: 1014–1020.
33. FitzGerald JD, Dalbeth N, Mikuls T et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care Res (Hoboken) 2020; 72: 744–760.
34. Hidalgo-Mora JJ, García-Vigara A, Sánchez-Sánchez ML, García-Pérez MÁ, Tarín J, Cano A. The Mediterranean diet: A historical perspective on food for health. Maturitas 132 2020 65–69.
35. Yokose C, McCormick N, Rai SK et al. Effects of low-fat, mediterranean, or low-carbohydrate weight loss diets on serum urate and cardiometabolic risk factors: A secondary analysis of the dietary intervention randomized controlled trial (direct). Diabetes Care 2020; 43: 2812–2820.
36. Guasch-Ferré M, Bulló M, Babio N et al. Mediterranean diet and risk of hyperuricemia in elderly participants at high cardiovascular risk. Journals of Gerontology - Series A Biological Sciences and Medical Sciences 2013; 68: 1263–1270.
37. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Purine-Rich Foods, Dairy and Protein Intake, and the Risk of Gout in Men. New England Journal of Medicine 2004; 350: 1093–1103.
38. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63: 3136–3141.
39. Zhang Y, Chen C, Choi H et al. Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis 2012; 71: 1448–1453.
40. Choi HK, McCormick N, Lu N, Rai SK, Yokose C, Zhang Y. Population Impact Attributable to Modifiable Risk Factors for Hyperuricemia. Arthritis and Rheumatology 2020; 72: 157–165.

41. Glynn RJ, Campion EW, Silbert JE. Trends in serum uric acid levels. Arthritis Rheum 1983; 26: 87–93.
42. Maglio C, Peltonen M, Neovius M et al. Effects of bariatric surgery on gout incidence in the Swedish Obese Subjects study: A non-randomised, prospective, controlled intervention trial. Ann Rheum Dis 2017; 76: 688–693.
43. Yeo C, Kaushal S, Lim B et al. Impact of bariatric surgery on serum uric acid levels and the incidence of gout—A meta-analysis. Obesity Reviews 2019; 20: 1759–1770.
44. Lu J, Bai Z, Chen Y et al. Effects of bariatric surgery on serum uric acid in people with obesity with or without hyperuricaemia and gout: a retrospective analysis. Rheumatology (United Kingdom) 2021; 60: 3628–3634.
45. Romero-Talamás H, Daigle CR, Aminian A, Corcelles R, Brethauer SA, Schauer PR. The effect of bariatric surgery on gout: A comparative study. Surgery for Obesity and Related Diseases 2014; 10: 1161–1165.
46. Choi HK, Curhan G. Beer, liquor, and wine consumption and serum uric acid level: The Third National Health and Nutrition Examination Survey. Arthritis Care and Research 51 2004 1023–1029.
47. Choi HK, Atkinson K, Karlson EW, Willett W, Curhan G. Alcohol intake and risk of incident gout in men: A prospective study. Lancet 2004; 363: 1277–1281.
48. Ralston SH, Capell HA, Sturrock RD. Alcohol and response to treatment of gout. Br Med J (Clin Res Ed) 1988; 296: 1641–1642.
49. Richette P, Doherty M, Pascual E et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Annals of the Rheumatic Diseases 76 2017 29–42.
50. Tai CJ, Wu CC, Lee KT et al. The Impact of Urate-Lowering Therapy in Post-Myocardial Infarction Patients: Insights From a Population-Based, Propensity Score-Matched Analysis. Clin Pharmacol Ther 2022; 111: 655–663.
51. Luo Y, Song Q, Li J et al. Effects of uric acid-lowering therapy (ULT) on renal outcomes in CKD patients with asymptomatic hyperuricemia: a systematic review and meta-analysis. BMC Nephrol 2024; 25.
52. Kelkar A, Kuo A, Frishman WH. Allopurinol as a cardiovascular drug. Cardiology in Review 19 2011 265–271.
53. Richette P. Allopurinol and risk of myocardial infarction. Heart 101 2015 659–660.
54. Mellin V, Isabelle M, Oudot A et al. Transient reduction in myocardial free oxygen radical levels is involved in the improved cardiac function and structure after long-term allopurinol treatment initiated in established chronic heart failure. Eur Heart J 2005; 26: 1544–1550.
55. Qazi SU, Qamar U, Maqsood MT et al. Efficacy of Allopurinol in Improving Endothelial Dysfunction: A Systematic Review and Meta-Analysis. High Blood Pressure and Cardiovascular Prevention 30 2023 539–550.
56. Rødevand E, Sletvold O, Kvande KT. Bivirkninger av allopurinol. Tidsskrift for den Norske Laegeforening 2004; 124: 2618–2619.
57. Quach C, Galen BT. HLA-B*5801 testing to prevent allopurinol hypersensitivity syndrome a teachable moment. JAMA Internal Medicine 178 2018 1258–1259.
58. Shibagaki Y, Ohno I, Hosoya T, Kimura K. Safety, efficacy and renal effect of febuxostat in patients with moderate-to-severe kidney dysfunction. Hypertension Research 2014; 37: 919–925.
59. Hira D, Chisaki Y, Noda S et al. Population pharmacokinetics and therapeutic efficacy of febuxostat in patients with severe renal impairment. Pharmacology 2015; 96: 90–98.

60. Xie H, Hu N, Pan T, Wu JC, Yu M, Wang DC. Effectiveness and safety of different doses of febuxostat compared with allopurinol in the treatment of hyperuricemia: a meta-analysis of randomized controlled trials. BMC Pharmacol Toxicol 2023; 24.
61. Kim LH, Kang SM, Whang J, Kwon KW, Shin SJ. Novel Antibacterial Activity of Febuxostat, an FDA-Approved Antigout Drug against Mycobacterium tuberculosis Infection. Antimicrob Agents Chemother 2022; 66.
62. Si X, Huang L, Ding Q et al. Comparison of clinical and economic evaluation between selected generic and original febuxostat tablets in Chinese gout patients with hyperuricemia A real-world multicenter retrospective study. Medicine (United States) 2024; 103: E37081.
63. Chohan S. Safety and efficacy of febuxostat treatment in subjects with gout and severe allopurinol adverse reactions. Journal of Rheumatology 2011; 38: 1957–1959.
64. Becker MA, Schumacher HR, Espinoza LR et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: The CONFIRMS trial. Arthritis Res Ther 2010; 12.
65. Yu KH, Lai JH, Hsu PN, Chen DY, Chen CJ, Lin HY. Safety and efficacy of oral febuxostat for treatment of HLA-B*5801-negative gout: a randomized, open-label, multicentre, allopurinol-controlled study. Scand J Rheumatol 2016; 45: 304–311.
66. Maeda K, Tian Y, Fujita T et al. Inhibitory effects of p-aminohippurate and probenecid on the renal clearance of adefovir and benzylpenicillin as probe drugs for organic anion transporter (OAT) 1 and OAT3 in humans. European Journal of Pharmaceutical Sciences 2014; 59: 94–103.
67. Frieden TR, Harold Jaffe DW, Rasmussen SA et al. Sexually Transmitted Diseases Treatment Guidelines, 2015 Morbidity and Mortality Weekly Report CONTENTS (Continued) Centers for Disease Control and Prevention MMWR Editorial and Production Staff (Serials) MMWR Editorial Board. 2015.
68. Guo L, Yang Y, Yang L et al. Comparative study of the effects of baicalin and probenecid on microRNA expression profiles in porcine aortic vascular endothelial cells infected by Glaesserella parasuis. BMC Vet Res 2025; 21: 237.
69. Bergeron HC, Crabtree J, Nagy T, Martin DE, Tripp RA. Probenecid Inhibits Human Metapneumovirus (HMPV) Replication In Vitro and in BALB/c Mice. Viruses 2024; 16.
70. Murray J, Martin DE, Hosking S, Orr-Burks N, Hogan RJ, Tripp RA. Probenecid Inhibits Influenza A(H5N1) and A(H7N9) Viruses In Vitro and in Mice. Viruses 2024; 16.
71. Pui K, Gow PJ, Dalbeth N. Efficacy and tolerability of probenecid as urate-lowering therapy in gout; Clinical experience in high-prevalence population. Journal of Rheumatology 2013; 40: 872–876.
72. Boger WP, Strickland SC. Probenecid (benemid): Its Uses and Side-Effects in 2,502 Patients. AMA Arch Intern Med 1955; 95: 83–92.
73. Padda IS, Bhatt R, Patel P, Parmar M. Pegloticase. 2025.
74. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011; 63: 3136–3141.
75. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. Journal of Rheumatology 2000; 27: 1501–1505.
76. Hazard A, Bourrion B, Dechaine F, Fournier L, François M. Lack of evidence for allopurinol for the prevention of a first gout attack in asymptomatic hyperuricemia: a systematic review. European Journal of Clinical Pharmacology 76 2020 897–899.

77. Zhang WZ. Why does hyperuricemia not necessarily induce gout? Biomolecules 11 2021 1–11.
78. Cabău G, Crișan TO, Klück V, Popp RA, Joosten LAB. Urate-induced immune programming: Consequences for gouty arthritis and hyperuricemia. Immunological Reviews 294 2020 92–105.
79. Hsu WL, Li SY, Liu JS et al. High uric acid ameliorates indoxyl sulfate-induced endothelial dysfunction and is associated with lower mortality among hemodialysis patients. Toxins (Basel) 2017; 9.
80. Luo Y, Song Q, Li J et al. Effects of uric acid-lowering therapy (ULT) on renal outcomes in CKD patients with asymptomatic hyperuricemia: a systematic review and meta-analysis. BMC Nephrol 2024; 25.
81. Yao X, Cai X, Zhang S et al. Mendelian randomization study of serum uric acid levels and urate-lowering drugs on pulmonary arterial hypertension outcomes. Sci Rep 2025; 15: 4460.