Innovative Approaches to Managing Hyperuricemia: Treatments and Emerging Therapies

Emily Daum*, Yenna Choi*, Yanfei Qi, MD, PhD, MS*

*Department of Pharmacology, Duquesne University Nasuti College of Osteopathic Medicine

DUQUESNE UNIVERSITY
Nasuti College of Osteopathic Medicine

ABSTRACT

- Hyperuricemia, defined by elevated serum urate levels, increases the risk of gout and is associated with cardiometabolic diseases (**Figure 1**).
- Although current urate-lowering therapies such as xanthine oxidase inhibitors and uricosurics are first-line treatments, their use can be limited by adverse effects, contraindications, resistance, and cost.
- Emerging therapies such as URAT1 inhibitors (dotinurad, AR882), novel xanthine oxidase inhibitors (tigulixostat), infusion therapies (SEL-212), and NLRP3 inflammasome inhibitors (dapansutrile) demonstrate significant urate-lowering and anti-inflammatory potentials in recent studies.
- Additionally, nutraceuticals and repurposed therapies such as Uricemin®, quercetin phytosome, tart cherry products, and prednisone show urate-lowering and metabolic benefits.
- Together, these advances suggest a shift towards more diverse and individualized treatment strategies for hyperuricemia.

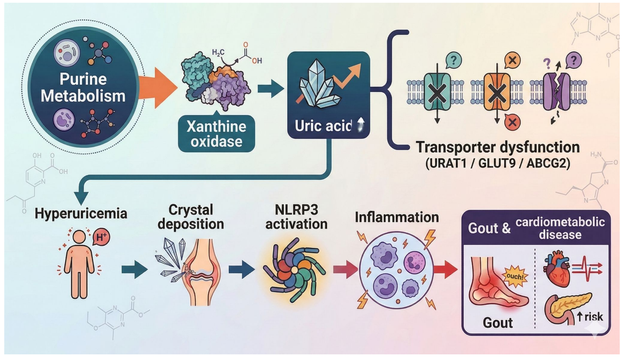

Figure 1: Image generated by Gemini detailing the metabolism and downstream effects of uric acid

BACKGROUND

Definition & Pathophysiology

Hyperuricemia is defined as serum uric acid levels exceeding the urate solubility threshold of ~6.8 mg/dL.[1] Altered renal urate transporters via URAT1, GLUT9, ABCG2, combined with uric acid production by xanthine oxidase, contributes to serum urate accumulation and monosodium urate crystal formation.[2] Monosodium urate crystals activate the NLRP3 inflammasome in macrophages, leading to IL-1β-mediated inflammation.[1]

Epidemiology

Hyperuricemia affects approximately 20-21% of adults in the United States, with increase prevalence globally[1]. Rates are higher in men, while estrogen provides partial protection in premenopausal women.[1]

Clinical Implication

Elevated urate promotes crystal deposition, triggering inflammation, endothelial dysfunction, and tissue injury.[2] Hyperuricemia is strongly associated with gout and cardiometabolic conditions including metabolic syndrome, hypertension, obesity, diabetes, and chronic kidney disease.[2]

Challenges in Current Treatment

Management is limited to poor adherence, delayed symptom relief, and the frequently asymptomatic nature of hyperuricemia.[3] Treatment decisions are further complicated by renal impairment, genetic variability and comorbidities, and limited long-term data on treating asymptomatic hyperuricemia.[4,5] Current treatments are also limited to certain molecular targets (**Figure 2**).

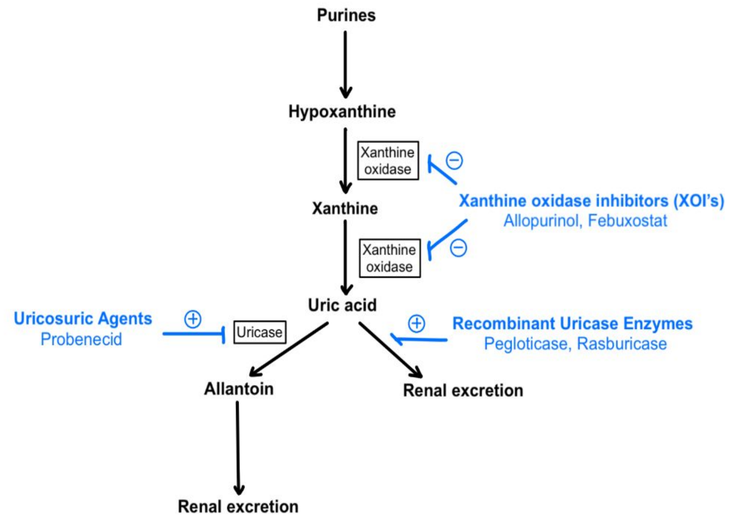

Figure 2: Targets of current FDA-approved urate-lowering therapies

OBJECTIVES

This literature review aims to summarize the pathophysiology, clinical implication, and emerging therapeutic strategies for hyperuricemia, with a focus on novel pharmacologic agents, repurposed drugs, and nutraceuticals that may address limitations of current urate-lowering therapies.

METHODS

Primary Data Source

>200 studies identified from **ClinicalTrials.gov** using NCT records related to hyperuricemia.

Dataset Development

Created a structured dataset capturing mechanism of action, study purpose, and reported outcomes.

Study Organization

Trials grouped by therapeutic mechanism, which served as the framework for analysis.

Supplementary Search and Source Refinement

Additional literature and databases were reviewed to identify missing or unpublished results. Some relevant studies were indexed under “gout” rather than “hyperuricemia,” highlighting the need for broader search strategies.

RESULTS

Our review of current literature and ongoing clinical trials has identified several emerging therapies that demonstrate significant urate-lowering potential through different mechanisms including urate transport inhibition, xanthine oxidase inhibition, enzymatic degradation, and anti-inflammatory properties.

RESULTS CONT.

- ***URAT1 inhibitors*** showed great efficacy in reducing serum uric acid (sUA) levels.
  - **Dotinurad** achieved sUA levels ≤6 mg/dL in 73.6% of patients within 24 weeks, compared with febuxostat, for which only 38.1% of patients reached equivalent levels in a Phase 3 trial involving 451 patients with gout.[6]
  - **Pozdeutinurad** (AR882) dosed at 75mg lowered the median sUA from 8.6 mg/dL to 3.5 mg/dL, with approximately 89% of patients reaching a sUA ≤6 mg/dL after 12 weeks.[7]
  - **Lingdolinurad** (ABP-671) and **ruzinurad** (SHR4640) achieve ideal sUA levels within short intervals due to their rapid-acting nature and mild, self-limiting adverse effects.[8]
- ***New xanthine oxidase inhibitors* (XOi)**
  - **Tigulixostat,** a potent non-purine selective XOi, reduced sUA over 12 weeks, with 47.1% of patients on 50 mg, 44.7% on 100 mg, and 62.2% on 200 mg achieving target sUA levels <5.0 mg/dL.[9]
- ***Advances in repurposed drugs and nutraceuticals*** are changing the field of hyperuricemia treatment.
  - **Uricemin®**, a flavonoid-based compound, lowered sUA below 6.5 mg/dL in all participants with borderline hyperuricemia.[10]
  - **Quercetin Phytosome™**, another flavonoid, reduced urate by 15.2% in healthy men and 13.8% in healthy women, and improved triglycerides.[11]
  - **Tart cherry juice** lowered urate by 19.2% while also proving useful in decreasing pro-inflammatory markers such as hs-CRP.[12]
  - **Other nutraceutical therapies,** including plant extracts, seed oils, prebiotics and more, may provide antioxidant properties, exert antioxidant and anti-inflammatory effects, function as prebiotics, and increase urinary pH, representing therapeutic approaches to hyperuricemia.
  - **Prednisone**, a glucocorticoid used widely for many inflammatory conditions, reduced sUA levels and improved renal function in patients with both congestive heart failure and hyperuricemia.[13]
- ***NLRP3 inflammasome inhibitors:***
  - **Dapansutrile**, an oral selective NLRP3 inflammasome inhibitor, was well tolerated and significantly reduced joint pain and inflammation in patients with acute gout flares within 7 days in a Phase 2a trial.[14]

CONCLUSIONS

- Although current treatments effectively lower sUA, available therapeutic options remain limited due to factors such as cost, safety profiles, and potential contraindications.
- The management of hyperuricemia is expanding beyond traditional therapies.
- Emerging therapies aim to broaden and optimize treatment strategies while supporting individualized patient care.
- New pharmacologic agents, nutraceuticals, and repurposed drugs are being investigated to target additional mechanisms in urate metabolism and inflammatory pathways.

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