Beyond Gout: The Cardiovascular Impact of Hyperuricemia and Its Role in Atherogenesis

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Abstract

Background: Atherosclerosis is a chronic inflammatory disease of the arterial wall and remains a leading cause of morbidity and mortality. Hyperuricemia-defined as elevated serum uric acid-has recently been implicated as a potential independent contributor to atherosclerotic cardiovascular disease (ASCVD).
Aim: This narrative review aims to explore the interrelationship between hyperuricemia and atherosclerosis by examining shared mechanisms of vascular injury, epidemiological evidence, and implications for management.
Methods: A comprehensive computer-based literature search was conducted using PubMed, Scopus, Web of Science and the Cochrane Library from January 2005 to September 2025. Keywords included atherosclerosis, hyperuricemia, gout, peripheral artery disease, and coronary artery disease. No restrictions were placed on language or study design. Reference lists of retrieved articles were manually screened for additional studies. In total, 36 articles met the inclusion criteria for this review.
Results: The evidence supports multiple mechanistic links: elevated uric acid promotes endothelial dysfunction, oxidative stress, nitric oxide depletion, activation of urate transporters (e.g., URATv1), and xanthine oxidase–mediated reactive oxygen species generation. Epidemiologic studies demonstrate associations between higher serum uric acid and increased risks of coronary heart disease incidence and mortality, stroke, and peripheral arterial disease; some data suggest stronger associations in women. Therapeutic interventions (e.g., xanthine oxidase inhibitors) may confer vascular benefit beyond urate lowering
Conclusions: Hyperuricemia and atherosclerosis are inter-related through overlapping molecular and inflammatory pathways. Considering serum uric acid as a modifiable cardiovascular risk factor may yield opportunities for earlier detection and prevention of ASCVD. Further prospective trials are needed to determine whether urate-lowering therapy directly reduces atherosclerotic events. (**TCM-GMJ June 2026; 12 (2): P16-P21)**

Keywords: Atherosclerosis; Hyperuricemia; Uric Acid; Endothelial Dysfunction; Xanthine Oxidase; Cardiovascular Disease.

Introduction

Atherosclerosis is a chronic inflammatory disease of the arterial wall and remains the leading cause of morbidity and mortality worldwide, accounting for nearly 50% of all deaths in Western societies. It is primarily a lipid-driven process initiated by the subendothelial accumulation of low-density lipoprotein (LDL) and remnant lipoprotein particles. This deposition triggers endothelial activation and an inflammatory cascade in focal regions of arteries, particularly at sites of disturbed or non-laminar blood flow such as arterial bifurcations. Atherosclerosis constitutes the pathophysiological basis of atherosclerotic cardiovascular disease (ASCVD), which clinically manifests as myocardial infarction, ischemic stroke, and peripheral arterial disease [1].

Hyperuricemia, defined as a serum uric acid concentration exceeding 6 mg/dL in women and 7 mg/dL in men, affects approximately 38 million individuals in the United States. Although most individuals are asymptomatic, growing evidence implicates elevated uric acid levels in the pathogenesis of cardiovascular, renal, and metabolic disorders. Approximately one-third of serum uric acid derives from dietary purines, while the remaining two-thirds are produced endogenously. Elevated levels may also occur in high cell turnover states—such as hemolysis, rhabdomyolysis, or tumor lysis syndrome—or due to impaired renal excretion associated with genetic disorders, chronic kidney disease, or metabolic syndrome. Roughly two-thirds of uric acid is eliminated through the kidneys and one-third via the gastrointestinal tract; however, these proportions may vary depending on comorbidities or medication use[2].

Given their shared metabolic and inflammatory pathways, atherosclerosis and hyperuricemia may be patho-

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physiologically interconnected. Numerous epidemiological and clinical studies have reported a potential association between elevated serum uric acid levels and the risk of atherosclerotic cardiovascular events. For instance, the Rotterdam Study by Bos et al. demonstrated that hyperuricemia is an independent predictor of myocardial infarction and stroke[3]. This review aims to explore and synthesize current evidence regarding the potential pathophysiological links between hyperuricemia and atherosclerosis.

Methods

A comprehensive computer-based literature search was conducted for this narrative review using the PubMed, Scopus, Cochrane Library, and Web of Science databases to identify relevant studies. Publications from January 2005 to September 2025 were included. The search strategy combined the following keywords and MeSH terms: atherosclerosis, hyperuricemia, gout, peripheral artery disease, and coronary artery disease. No restrictions were applied regarding study design, language, or publication type.

To ensure comprehensiveness, relevant journals and conference proceedings were also manually screened, and the reference lists of all retrieved articles were examined to identify additional relevant studies. In total, 36 articles met the inclusion criteria and were selected for analysis. In sections addressing conservative treatment strategies, the authors also integrated their own clinical experience and practical insights into the management of hyperuricemia and atherosclerosis

Results and discussion

Atherosclerosis is a chronic inflammatory disease of the arterial wall, arising from the interplay of multiple modifiable and nonmodifiable risk factors. Modifiable factors include obesity, physical inactivity, dyslipidemia, smoking, and hypertension, as well as hyperuricemia, while nonmodifiables are age, genetic predisposition, and family history [4].

Specifically hyperuricemia arises from altered uric acid metabolism due to underexcretion, overproduction, or both, influenced by modifiable and nonmodifiable factors [5]. The relationship between hyperuricemia and atherosclerosis has gained attention as a key focus in preventive cardiovascular medicine. Hyperuricemia is strongly associated with hypertension [6], chronic kidney disease [7], type 2 diabetes mellitus [8], and metabolic syndrome [9]-all established contributors to atherosclerosis. Emerging evidence also suggests that hyperuricemia independently promotes cardiovascular disease, even in the absence of these traditional risk factors. These factors contribute to endothelial injury and dysfunction, initiating compensatory processes that culminate in the formation of atherosclerotic plaques.

Endothelial Activation and Dysfunction

Endothelial activation refers to a state in which endothelial cells acquire proinflammatory and procoagulant properties under the influence of oxidized lipoproteins and systemic cytokines [10,16,17] .This promotes adhesion molecule expression and facilitates recruitment of inflammatory cells into the vascular wall. Endothelial dysfunction (ED), considered an initiating event in atherogenesis, can be triggered by elevated uric acid, which stimulates the release of inflammatory mediators such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-β, chemokines, and adhesion molecules [10,16,17] .

Oxidative Stress and Nitric Oxide Depletion

Uric acid contributes to oxidative stress, inflammation, and endothelial injury [11,16,17] . During purine metabolism, xanthine oxidase (XO) converts xanthine to uric acid and superoxide, generating reactive oxygen species (ROS) [12,16,17] . Other major ROS sources include NADPH oxidase, lipoxygenase, myeloperoxidase, and uncoupled nitric oxide synthase (NOS) [13,16,17] .

Excess superoxide ($O_2^{\bullet-}$) combines with uric acid to reduce nitric oxide (NO) bioavailability, forming peroxynitrite ($ONOO^-$), a potent oxidant that damages DNA, lipids, and endothelial cells [14,16,17] . Peroxynitrite oxidizes tetrahydrobiopterin (BH_4), a critical eNOS cofactor, causing eNOS uncoupling-switching NO production to superoxide generation. This establishes a vicious cycle of oxidative stress, NO depletion, $ONOO^-$ formation, and progressive endothelial dysfunction [14,16,17] . Concurrent uric acid and superoxide production via XO activity therefore plays a key role in vascular injury [13,16,17] .

Role of Xanthine Oxidase in Vascular Injury

XO is located in the cytoplasm and on the endothelial cell surface. Circulating XO can bind endothelial glycosaminoglycans and undergo endocytosis, impairing NO-mediated vascular relaxation [15,16,17] . This provides a direct biochemical link between uric acid metabolism and endothelial dysfunction.

Uric Acid Transporters in Endothelial Cells

Endothelial cells express uric acid transporters, including URAT1 and URATv1. Their activation decreases NO bioavailability and increases ROS generation, contributing to endothelial dysfunction (19). In vitro studies show that uric acid reduces NO release and enhances C-reactive protein (CRP) production in human umbilical vein endothelial cells (HUVECs) via p38 and ERK44/42 MAP kinase pathways. These effects, which inhibit endothelial migration and proliferation, are reversed by probenecid, a uric acid transporter inhibitor [20,21] .

Similarly, Yui et al. demonstrated that uric acid–induced endothelial senescence and apoptosis are mitigated by probenecid, enalaprilat, or telmisartan. Uric acid rapidly increases ROS, upregulates renin–angiotensin system components, and elevates angiotensin II levels, all reversible by antioxidants such as N-acetylcysteine and tempol. These findings indicate that hyperuricemia mediates endothelial dysfunction via oxidative stress and renin–angiotensin system activation [22].

Recent studies confirm that URATv1 is the predominant endothelial uric acid transporter, as URATv1 mRNA is detected in HUVECs while URAT1 is absent [23]. Overall, intracellular uric acid uptake promotes inflammation and oxidative stress, driving endothelial dysfunction and accelerating atherosclerotic progression.

Studies were included if they examined the relationship between hyperuricemia and atherosclerosis or their associated cardiovascular complications, including coronary artery disease, cerebrovascular disease, and peripheral artery

disease. Eligible study types encompassed experimental and observational designs, such as randomized controlled trials, cohort studies, case-control studies, cross-sectional analyses, and relevant case reports. Review articles and meta-analyses were also considered if they offered additional insights into pathophysiological mechanisms or management strategies.

Exclusion criteria comprised studies unrelated to uric acid metabolism and atherosclerotic processes, publications lacking original data or full-text availability, non-English articles, duplicate publications, and abstracts without sufficient methodological details.

Despite already known association between hypertension and hyperuricemia, the last one is full of secrets and nowadays is just known as most common cause of inflammatory arthritis in the world wide. Urate-lowering therapy (ULT) remains underutilized despite long-standing recommendations from the American College of Rheumatology (ACR). The updated ACR guidelines emphasize earlier initiation, risk stratification, and optimized the levels of uric acid. In contrast, atherosclerosis-one of the leading causes of cardiovascular morbidity and mortality-has a more established and multifactorial therapeutic approach involving lifestyle modification, pharmacotherapy, and interventional procedures. This review summarizes the current ACR recommendations for gout management and outlines evidence-based treatment strategies for atherosclerosis.

Atherosclerosis Management

Atherosclerosis management is centered around comprehensive cardiovascular risk reduction through lifestyle changes:

- Diet: Adoption of the DASH diet or similar heart-healthy patterns.
- Physical activity: ≥150 minutes of moderate-intensity or ≥75 minutes of vigorous-intensity exercise weekly.
- Smoking cessation: Reduces endothelial injury and inflammatory burden.
- Sleep hygiene: Maintain 7–9 hours of sleep per night.
- Weight management: A reduction of 3–5% of body weight can significantly improve lipid and glucose metabolism.
- Alcohol moderation: ≤2 drinks/day for men, ≤1 drink/day for women.

Stress reduction: Improves both cardiovascular and emotional health [26–27].

Pharmacologic Interventions

- ACE inhibitors and β-blockers: Lower blood pressure and reduce cardiac workload [26,28].
- Antiplatelet and anticoagulant agents: Reduce risk of thrombotic complications [26,29].
- Calcium channel blockers: Induce vasodilation and lower systemic pressure.
- Antidiabetic agents: Improve metabolic control in diabetic patients with atherosclerosis.
- Nitrates (e.g., nitroglycerin): Relieve angina by dilating coronary arteries.
- Ranolazine: Alleviates symptoms of coronary microvascular disease [26,31].

Statins: First-line therapy for dyslipidemia and secondary prevention of atherosclerotic cardiovascular disease [26,30].

Procedural and Surgical Management

In patients with advanced or refractory disease, interventional or surgical options are indicated:

- Percutaneous coronary intervention (PCI) for coronary stenosis or occlusion.
- Coronary artery bypass grafting (CABG) for multivessel or left main coronary artery disease.
- Carotid endarterectomy or stenting for carotid artery stenosis.
- Coronary endarterectomy for severe, non-revascularizable angina.
- Peripheral angioplasty for lower limb arterial disease.

Bariatric surgery in severe obesity to reduce systemic inflammation and atherosclerotic risk [26,32].

Hyperuricemia Treatment

Indications for Urate-Lowering Therapy

ULT is recommended for patients presenting with:

- Two or more gout flare-ups per year,
- Tophaceous gout, or

Radiographic evidence of gout-related joint damage.

shared decision-making is advised when high-risk factors are present, such as:

- Serum urate level ≥9 mg/dL (0.54 mmol/L),
- History of urolithiasis, or

Chronic kidney disease (CKD) stage 3 or higher.

ULT has not demonstrated benefit in patients with asymptomatic hyperuricemia [24].

Timing of Initiation

According to ACR guidelines, ULT may be initiated during an acute flare-up, provided appropriate anti-inflammatory therapy is co-administered. Early initiation does not worsen or prolong symptoms and may enhance treatment adherence, as patients are often most motivated during exacerbations. Anti-inflammatory agents-such as colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs)-should be continued for three to six months following ULT initiation to prevent recurrence [24].

Management should also address comorbid conditions and lifestyle factors: reducing hypertension and lipid-lowering medications like fenofibrate, as well as lifestyle modification like Restriction of alcohol, purine-rich foods, and high-fructose corn syrup and Encouragement of weight reduction. [24–26]

Pilot studies suggest that lowering uric acid can result in an improvement in BP in obese adolescents with hyperuricemia and prehypertension or with newly diagnosed hypertension, and in adults with asymptomatic hyperuricemia [39]. Thats why we should incorporate ULT in Gout or Hypertension, but as well as in managing of Atherosclerosis and other cardio vascular disease.

Atherosclerosis imposes a substantial global burden on

cardiovascular health due to its pivotal role in the pathogenesis of major cardiovascular diseases (CVD), including coronary artery disease and heart failure. Extensive clinical and experimental evidence has confirmed the central role of inflammation in the development and progression of atherosclerosis. Consequently, there is a growing demand for preclinical research focused on atherosclerotic inflammation. A deeper understanding of the molecular and cellular mechanisms underlying inflammatory pathways in atherosclerosis will likely facilitate the identification of novel therapeutic targets with translational potential [33] .

Concurrently, hyperuricemia has emerged as a condition of increasing clinical importance. Its prevalence continues to rise worldwide, particularly in developed nations, and it significantly impairs quality of life. Uric acid (UA) exhibits complex biological activities, acting both as an antioxidant and as a pro-oxidative, pro-inflammatory, nitric oxide–modulating, and immune-modifying molecule. These multifaceted roles are relevant in both physiological and pathological settings. Although previous studies have identified the involvement of hyperuricemia in numerous metabolic and signaling pathways, the precise mechanisms linking elevated UA levels to disease pathogenesis remain incompletely elucidated. Moreover, the interplay between genetic predisposition and environmental factors in determining UA metabolism warrants detailed investigation [34] .

Several epidemiological studies have identified elevated serum UA as a potential biomarker and predictor of cardiovascular disease. Available evidence suggests that hyperuricemia contributes to atherogenesis through multiple mechanisms: impairment of lipid metabolism, reduction of nitric oxide synthesis in endothelial cells, promotion of vascular smooth muscle cell proliferation, and amplification of inflammatory responses. In patients with endothelial dysfunction and coronary artery lesions, elevated UA is considered an independent predictor of disease severity. Recent studies further demonstrate that treatment with xanthine oxidase (XO) inhibitors provides dual benefits-reducing serum UA levels and attenuating atherosclerotic burden [35] .

Given that hyperuricemia is a well-recognized risk factor for hypertension, diabetes mellitus, metabolic syndrome, and chronic kidney disease—all of which predispose to atherosclerosis—the coexistence of these conditions is unsurprising. However, establishing a direct association between hyperuricemia and atherosclerosis, independent of these comorbidities, is crucial. Such evidence may pave the way for a new era of preventive cardiovascular medicine and inform more comprehensive management strategies.

The etiological framework presented earlier provides a flexible foundation for examining this relationship, which is further supported by several key clinical studies. Dr. Seo Young Kim and colleagues analyzed 26 eligible studies encompassing 402,997 adults and demonstrated that hyperuricemia was associated with increased risks of coronary heart disease (CHD) incidence (unadjusted risk ratio [RR] 1.34; 95% confidence interval [CI] 1.19–1.49) and CHD mortality (unadjusted RR 1.46; 95% CI 1.20–1.73). After adjustment for potential confounders, the pooled RR was 1.09 (95% CI 1.03–1.16) for CHD incidence and 1.16 (95% CI 1.01–1.30) for CHD mortality. For each 1 mg/dL increase in serum UA, the pooled multivariate RR for CHD mortality was 1.12 (95% CI 1.05–1.19). Subgroup analysis revealed no significant association between hyperuricemia and CHD in men, but a significantly increased risk in women (RR 1.67; 95% CI 1.30–2.04) [36].

In another study, Xingchen Du and colleagues included 389 patients with hyperuricemia from the NHANES database. Logistic regression identified age, serum creatinine, glucose, serum uric acid, and a history of gout as predictive factors for atherosclerotic cardiovascular disease (ASCVD). Using these parameters, the authors constructed and validated a nomogram model, achieving excellent discrimination with area under the curve (AUC) values of 0.943, 0.735, and 0.664 in derivation, internal validation, and external validation cohorts, respectively. The Hosmer–Lemeshow test ($p = .568, .600, .763$) and calibration curves indicated strong agreement between predicted and observed outcomes, while decision curve analysis confirmed its clinical applicability. This model offers a valuable tool for early identification of high-risk ASCVD patients among individuals with hyperuricemia [37].

A longitudinal study by Maria Perticone et al. followed participants for a mean duration of 9.5 ± 3.1 years, documenting 424 new fatal and non-fatal events (2.71%), including 250 coronary (1.59%), 118 cerebrovascular (0.75%), and 56 deaths (0.40%), which is represented in figure 1. Notably, females exhibited a significantly higher incidence of major adverse cardiovascular events (MACE) compared to males (3.08% vs 2.33%; $p = 0.001$), including both coronary (1.82% vs 1.36%; $p = 0.014$) and cerebrovascular (0.93% vs 0.57%; $p = 0.006$) events, though overall mortality did not differ significantly (0.38% vs 0.32%; $p = 0.555$) [38].

Furthermore, figure 2 shows analysis of receiver operating characteristic (ROC) curves demonstrated that serum UA was a reliable predictor of MACE, coronary, and cerebrovascular events in both sexes. The optimal serum UA cutoff for predicting these outcomes ranged between 4.8–5.2 mg/dL in women and 5.3–5.6 mg/dL in men [38].

These findings collectively reinforce the notion that elevated UA levels, even within near-normal ranges, are linked to increased cardiovascular risk and that this association appears more pronounced among women

Overall, elevated uric acid levels can influence the onset and progression of coronary heart disease **(**CHD) by impairing vascular endothelial function, increasing oxidative stress, and activating inflammatory pathways. Consequently, it is important for clinicians, researchers, and patients to work collaboratively to develop improved strategies for preventing and managing hyperuricemia. Such efforts may lead to safer and more effective treatment options for individuals with CHD.

Conclusion

Atherosclerosis and hyperuricemia, though distinct clinical entities, share intersecting biochemical, inflammatory

and vascular-injury pathways. Uric acid is not merely a metabolic by-product but an active participant in endothelial dysfunction, oxidative stress, NO-depletion and vascular smooth muscle proliferation, all of which promote atherosclerotic progression. Epidemiologic evidence consistently demonstrates that elevated serum uric acid is an independent predictor of coronary heart disease, cerebrovascular events and cardiovascular mortality, especially in women. Moreover, the prognostic utility of uric acid levels for ASCVD risk stratification is emerging.

Clinicians should consider serum uric acid as a modifiable cardiovascular risk marker in at-risk patients. Early detection of hyperuricemia and prompt management may offer dual benefits: reducing gout-related morbidity and mitigating the burden of atherosclerotic cardiovascular disease. Nevertheless, further prospective trials are required to establish causality and to determine whether urate-lowering therapy directly translates into cardiovascular event reduction.

Table 1 shows the summarization of medication and dosages which are used to treat hyperuricemia/Gout

Medications	Mechanism of action	Dosage	Special considerations
Allopurinol	Xanthine oxidase inhibitor	Start at ≤100 mg daily (or lower in ≥ stage 3 chronic kidney disease); dosage can be titrated up to 800 mg daily	Test for HLA-B*5801 in patients of Southeast Asian or African American descent
Febuxostat	Xanthine oxidase inhibitor	Start at ≤40 mg daily; maximum dosage is 80 mg daily in the United States	Switch to another agent in patients with a history of cardiovascular disease or a new cardiovascular event
Probenecid	uricosuric	Start at 100 mg once or twice daily; can be increased to 1 g twice daily	No evidence for checking urinary uric acid
Pegloticase	uricase	8 mg intravenously every 2 weeks	Not recommended as first-line option

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