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Mini Review

Uric Acid and Circulatory Diseases: From Biomarker to Potential Cardiovascular Risk Factor

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Abstract

Background: Hyperuricemia has traditionally been regarded as a biochemical marker of gout and urate crystal deposition diseases. In recent years, increasing experimental and epidemiological evidence has suggested a broader role for serum uric acid (SUA) in the development and progression of cardiovascular and circulatory disorders.

Objective: To review the current evidence linking hyperuricemia with vascular disease and to discuss the potential pathophysiological mechanisms underlying its association with cardiovascular morbidity and mortality.

Methods: A narrative review of experimental, epidemiological, and clinical studies evaluating the relationship between serum uric acid and major circulatory diseases, including hypertension, coronary artery disease, heart failure, cerebrovascular disease, and peripheral arterial disease.

Results: Elevated SUA levels are associated with endothelial dysfunction, oxidative stress, chronic inflammation, vascular smooth muscle proliferation, and activation of the renin-angiotensin-aldosterone system. These mechanisms contribute to vascular remodeling and atherosclerosis. Numerous observational studies have demonstrated independent associations between hyperuricemia and arterial hypertension, coronary artery disease, heart failure, stroke, peripheral arterial disease, and cardiovascular mortality. Furthermore, hyperuricemia frequently coexists with chronic kidney disease, diabetes mellitus, obesity, and metabolic syndrome, supporting its role within the emerging cardio-renal-metabolic continuum.

Conclusions: Hyperuricemia is increasingly recognized as a potentially modifiable cardiovascular risk factor rather than merely a marker of comorbidity. Although definitive evidence of causality remains incomplete, current data support a significant contribution of uric acid to vascular damage and circulatory disease progression. Future randomized clinical trials are needed to establish whether urate-lowering therapies can improve cardiovascular outcomes beyond their established role in gout management.

Introduction

For many years, serum uric acid (SUA) was considered merely the biochemical hallmark of gout and urate crystal deposition disorders. During the last two decades, growing epidemiological, experimental, and clinical evidence has identified hyperuricemia as a potential contributor to cardiovascular and vascular disease. Elevated SUA levels have been associated with hypertension, coronary artery disease, heart failure, atrial fibrillation, peripheral arterial disease, stroke, and cardiovascular mortality [1-3]. Although the causative role of uric acid remains debated, mounting evidence suggests that hyperuricemia may actively participate in vascular injury through endothelial dysfunction, oxidative stress, inflammation, and activation of neurohormonal pathways [1,2].

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Pathophysiological basis of vascular damage

Uric acid exerts paradoxical biological effects. In the extracellular environment it acts as an antioxidant, whereas intracellular accumulation induces oxidative stress, inflammation, and endothelial injury. Experimental studies have demonstrated that elevated uric acid reduces nitric oxide bioavailability, impairs endothelial-dependent vasodilation, and stimulates vascular smooth muscle cell proliferation [1,2,4].

Furthermore, hyperuricemia activates the renin-angiotensin-aldosterone system (RAAS), promotes insulin resistance, and enhances oxidative stress through increased xanthine oxidase activity. These mechanisms contribute to vascular remodeling and atherosclerosis [1,2-8].

Hyperuricemia and arterial hypertension

Among cardiovascular disorders, the strongest evidence linking uric acid to disease development concerns arterial hypertension. Experimental and clinical studies have shown that elevated SUA precedes the development of hypertension, particularly in younger individuals [2,7].

Reduced nitric oxide synthesis together with RAAS activation results in vasoconstriction and microvascular damage, promoting increases in blood pressure. Long-standing hyperuricemia induces irreversible arteriolosclerosis and salt-sensitive hypertension [2,7].

Several large observational studies have confirmed that increasing SUA concentrations independently predict incident hypertension after adjustment for traditional cardiovascular risk factors [2,7].

Coronary artery disease and atherosclerosis

Hyperuricemia has consistently been associated with coronary artery disease (CAD) and adverse cardiovascular outcomes. Elevated SUA correlates with endothelial dysfunction, increased carotid intima-media thickness, coronary calcification, and accelerated atherosclerosis [1,3,4]. Uric acid contributes to plaque formation through oxidative stress, chronic inflammation, platelet activation, and enhanced low-density lipoprotein oxidation [1,4,5].

Recent systematic reviews support a significant association between hyperuricemia and coronary heart disease, myocardial infarction, and cardiovascular mortality [3,6]. These findings suggest that uric acid may represent more than a simple biomarker of cardiovascular risk.

Heart failure

Hyperuricemia is highly prevalent among patients with heart failure and is recognized as a marker of disease severity and poor prognosis [2,3].

Increased xanthine oxidase activity, tissue hypoxia, oxidative stress, and reduced renal perfusion contribute to elevated SUA concentrations in these patients [2,8]. Several large cohorts have demonstrated that higher SUA levels independently predict hospitalization, progression of heart failure, and cardiovascular mortality [2,3]. Data from the URRAH Project demonstrated that hyperuricemia and increased left ventricular mass independently predict cardiovascular death [9].

Cerebrovascular disease and stroke

An increasing body of evidence supports an association between hyperuricemia and cerebrovascular disease. Elevated SUA levels have been linked to both stroke incidence and stroke-related mortality [3,10]. Potential mechanisms include endothelial dysfunction, atherosclerosis, platelet activation, increased arterial stiffness, and chronic vascular inflammation [1,3,4].

A recent meta-analysis involving more than 700,000 individuals demonstrated a significant association between hyperuricemia and stroke risk, as well as stroke-related mortality [10].

Peripheral arterial disease

Peripheral arterial disease (PAD) appears to share common pathophysiological pathways with hyperuricemia. Elevated SUA contributes to endothelial dysfunction, oxidative stress, chronic inflammation, and impaired peripheral circulation [3,4]. Hyperuricemia may therefore be considered a marker of diffuse systemic atherosclerosis and global vascular burden [3,5].

Hyperuricemia in the cardio-renal-metabolic continuum

The emerging concept of Cardio-Renal-Metabolic (CRM) Syndrome provides a unifying framework linking metabolic disorders, chronic kidney disease, and cardiovascular disease [8]. Hyperuricemia frequently coexists with obesity, diabetes mellitus, insulin resistance, metabolic syndrome, and CKD [7,8]. Reduced renal excretion in CKD further amplifies SUA levels, creating a vicious cycle of vascular and renal injury [7,8]. Within this integrated model, uric acid may function both as a biomarker and as a pathogenic mediator linking renal dysfunction, metabolic derangements, and cardiovascular disease [1,3,8].

Therapeutic implications

Whether urate-lowering therapy can reduce cardiovascular risk remains controversial. Observational studies suggest potential cardiovascular benefits from xanthine oxidase inhibitors, particularly allopurinol, but randomized clinical trials have yielded inconsistent results [2,7]. Current international recommendations support treatment of symptomatic hyperuricemia, gout, urate nephrolithiasis, and selected high-risk patients, whereas treatment of asymptomatic hyperuricemia remains debated [2,7,8]. Future prospective studies are needed to determine whether lowering serum uric acid can improve hard cardiovascular outcomes beyond the management of established urate-related disorders [1,3].

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Discussion

The present review highlights the growing body of evidence supporting a significant association between hyperuricemia and the development of circulatory diseases. Traditionally regarded as a biochemical consequence of purine metabolism and a hallmark of gout, serum uric acid (SUA) has progressively emerged as a potential contributor to cardiovascular pathology. The increasing consistency of epidemiological, experimental, and clinical data suggests that uric acid may represent not only a marker of systemic risk but also an active participant in vascular injury and disease progression [1-3]. One of the most compelling observations is the strong association between hyperuricemia and arterial hypertension. Several longitudinal studies have demonstrated that elevated SUA frequently precedes the onset of hypertension, particularly in younger populations, supporting the hypothesis of a pathogenic role in the early phases of vascular dysfunction [2,7]. Experimental models indicate that uric acid reduces endothelial nitric oxide availability, induces microvascular rarefaction, and activates the renin-angiotensin-aldosterone system, leading to increased peripheral vascular resistance and sodium retention. Over time, these functional abnormalities may evolve into structural vascular changes, including arteriolosclerosis and irreversible salt-sensitive hypertension. Such observations support the concept that uric acid could be involved in the transition from reversible endothelial dysfunction to permanent vascular remodeling.

The association between hyperuricemia and atherosclerotic cardiovascular disease further strengthens the hypothesis of a mechanistic role for uric acid. Elevated SUA levels are consistently associated with markers of subclinical atherosclerosis, including carotid intima-media thickness, coronary artery calcification, endothelial dysfunction, and increased arterial stiffness [1,3,4]. Experimental evidence suggests that intracellular uric acid stimulates oxidative stress through xanthine oxidase activity, increases inflammatory cytokine production, promotes low-density lipoprotein oxidation, and enhances platelet activation [1,4,5]. These mechanisms contribute to all major stages of atherogenesis, from endothelial injury to plaque development and destabilization. Consequently, uric acid may be considered both a biomarker of vascular risk and a mediator amplifying proatherogenic pathways.

Heart failure represents another important clinical context in which uric acid appears to have prognostic significance. Hyperuricemia is highly prevalent across the spectrum of heart failure phenotypes and correlates with disease severity, hospitalization rates, and mortality [2,3]. Elevated uric acid levels in heart failure likely reflect a combination of enhanced xanthine oxidase activity, tissue hypoxia, oxidative stress, neurohormonal activation, and impaired renal clearance. However, accumulating data suggest that SUA is more than a passive marker of disease severity. The URRAH Project demonstrated that both hyperuricemia and increased left ventricular mass independently predict cardiovascular mortality, indicating that uric acid may identify patients with a particularly adverse cardiovascular phenotype [9]. The relationship between uric acid and myocardial remodeling deserves further investigation because it may reveal novel therapeutic targets for cardiovascular prevention.The cerebrovascular implications of hyperuricemia are equally noteworthy. Recent meta-analyses involving large populations have reported a significant association between elevated SUA levels and both incident stroke and stroke-related mortality [10]. Mechanistically, endothelial dysfunction, arterial stiffness, chronic vascular inflammation, and accelerated atherosclerosis likely contribute to cerebrovascular vulnerability. Although some earlier studies suggested a possible neuroprotective antioxidant role of uric acid during acute ischemic events, current evidence generally supports a detrimental effect of chronic hyperuricemia on cerebral vascular health [1,10]. This apparent paradox underscores the complexity of uric acid biology and the need to distinguish acute from chronic effects and extracellular from intracellular mechanisms.

An important aspect emerging from contemporary research is the integration of hyperuricemia within the broader Cardio-Renal-Metabolic (CRM) Syndrome framework. Hyperuricemia frequently coexists with chronic kidney disease, obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus, and hypertension [7,8]. This clustering raises the question of whether uric acid is simply a surrogate marker reflecting systemic metabolic dysfunction or an independent contributor to disease progression. Increasing experimental evidence favors the latter hypothesis. Reduced renal excretion and enhanced production of uric acid establish a vicious cycle in which renal dysfunction, inflammation, oxidative stress, and vascular injury reinforce one another. In this context, uric acid may serve as a central biological link connecting metabolic abnormalities, kidney disease, and cardiovascular outcomes [8]. The issue of causality remains one of the most debated topics in the field. An important source of uncertainty is the presence of potential confounding factors. Chronic kidney disease reduces renal urate excretion and frequently coexists with established cardiovascular risk factors. Similarly, diuretic therapy, particularly thiazide and loop diuretics, may increase serum uric acid concentrations independently of cardiovascular disease mechanisms. Obesity, insulin resistance, type 2 diabetes mellitus and metabolic syndrome are also strongly associated with both hyperuricemia and adverse cardiovascular outcomes. Therefore, residual confounding cannot be completely excluded in observational studies evaluating the relationship between serum uric acid and circulatory diseases.While observational studies consistently demonstrate independent associations between hyperuricemia and adverse cardiovascular outcomes, establishing direct causation remains challenging. Hyperuricemia often coexists with multiple cardiovascular risk factors, including obesity, diabetes, CKD, and hypertension, making residual confounding difficult to eliminate completely. Mendelian randomization studies have yielded mixed results, with some investigations supporting a causal role and others suggesting that uric acid may principally function as a marker of underlying metabolic disturbances [2,7]. While several Mendelian randomization studies have suggested a limited direct causal effect of uric acid itself, others have supported a contributory role through complex metabolic and renal pathways. Consequently, current genetic evidence remains insufficient to establish a definitive causal relationship.Therefore, despite substantial biological

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plausibility, definitive proof that hyperuricemia directly causes cardiovascular disease remains incomplete.This uncertainty is reflected in the therapeutic arena. Xanthine oxidase inhibitors, particularly allopurinol and febuxostat, effectively lower serum uric acid levels and are widely used in gout management. Observational studies have reported potential benefits on endothelial function, blood pressure control, and cardiovascular outcomes [2,7]. Nevertheless, randomized controlled trials have produced conflicting results, with some studies demonstrating improvement in surrogate cardiovascular endpoints and others failing to show significant reductions in major adverse cardiovascular events. These discrepancies may be related to differences in patient populations, baseline cardiovascular risk, duration of follow-up, and study design. Consequently, current guidelines generally recommend treatment of symptomatic hyperuricemia but do not universally endorse urate-lowering therapy solely for cardiovascular prevention.

From a clinical perspective, SUA measurement remains attractive because it is inexpensive, widely available, and reproducible. Incorporating uric acid into cardiovascular risk assessment may improve identification of high-risk individuals, particularly those with concomitant kidney disease or metabolic disorders. Furthermore, hyperuricemia may represent an easily measurable marker of the global cardiovascular burden within the cardio-renal-metabolic continuum. Future risk prediction models incorporating SUA alongside traditional cardiovascular risk factors may help refine preventive strategies and personalize clinical management.

Several limitations of the currently available evidence should be acknowledged. Most studies are observational, and heterogeneity exists regarding the definition of hyperuricemia, population characteristics, and adjustment for confounding variables. In addition, sex-specific differences in uric acid metabolism, genetic determinants of urate handling, and ethnic variability remain incompletely understood. Further mechanistic studies and large-scale randomized clinical trials are required to clarify whether uric acid is a modifiable therapeutic target capable of altering the natural history of cardiovascular disease.

Contemporary evidence increasingly supports the view that hyperuricemia is closely linked to vascular damage and circulatory disease. The biological mechanisms identified to date provide substantial plausibility for a contributory role of uric acid in endothelial dysfunction, hypertension, atherosclerosis, heart failure, and stroke. Although causality has not yet been definitively proven, hyperuricemia appears to occupy a potentially important position within the cardio-renal-metabolic continuum, although the relative contribution of uric acid as a causal factor versus a marker of underlying metabolic dysfunction remains incompletely defined.Future interventional studies will determine whether targeting uric acid can translate into meaningful reductions in cardiovascular morbidity and mortality, potentially transforming hyperuricemia from a marker of risk into a therapeutic target for cardiovascular prevention.

Conclusions

Hyperuricemia is increasingly recognized as an important component of cardiovascular risk assessment. Elevated serum uric acid is associated with hypertension, coronary artery disease, heart failure, stroke, and peripheral arterial disease through mechanisms involving oxidative stress, endothelial dysfunction, inflammation, and vascular remodeling [1-10]. Although definitive proof of causality remains unavailable, current evidence supports the concept that uric acid is more than a passive biomarker and may represent an active participant in the cardio-renal-metabolic continuum [1,3,8].

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