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Hyperuricemia and Cardiovascular Disease: Mechanisms, Associations, and Therapeutic Implications – A Literature Review

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Abstract

Introduction

Uric acid has emerged as a potential biomarker for cardiovascular risk. Hyperuricemia, described as an abnormally elevated concentration of uric acid in the bloodstream, has been associated with the development of cardiovascular diseases such as hypertension, atrial fibrillation, heart failure, and coronary heart disease. Recent studies have investigated the potential benefits of using uric acid-lowering therapy in slowing the progression of these diseases. In this review, we summarize current evidence on the impact of hyperuricemia on cardiovascular diseases and the effectiveness of urate-lowering therapy in affected patients.

Material and methods

Databases such as Pubmed and Google Scholar were used for this research with the key words: hyperuricemia, endothelial dysfunction, cardiovascular disease, allopurinol, febuxostat, SGLT2.

Results

Current evidence indicates a strong association between hyperuricemia and several cardiovascular diseases, including hypertension, atrial fibrillation, heart failure, and coronary artery disease. Observational and cohort studies consistently show that elevated serum uric acid levels are linked to a higher incidence and severity of these conditions. However, the effectiveness of urate-lowering therapy in improving cardiovascular outcomes remains inconsistent. While some studies report beneficial effects of agents such as allopurinol and SGLT2 inhibitors—particularly in reducing blood pressure or improving heart failure symptoms—other trials show no significant impact or even increased mortality

risk, especially with febuxostat.

Conclusions

Hyperuricemia appears to be a relevant marker and possible contributor to cardiovascular disease development, potentially through mechanisms involving oxidative stress, endothelial dysfunction, and systemic inflammation. Although uric acid-lowering therapies show promise in certain clinical settings, current findings are inconclusive and occasionally contradictory. Large-scale trials are needed to clarify the role of urate-lowering treatment in cardiovascular prevention and management.

Keywords

Uric acid, hyperuricemia, cardiovascular disease, hypertension, atrial fibrillation, heart failure, coronary artery disease, urate-lowering therapy

1. Introduction

Uric acid is produced through purine metabolism. Two purine nucleid acids, adenine and guanine, undergo a series of enzymatic reactions to form this end product. A key role is played by enzyme xanthine-oxidoreductase, which converts xanthine to uric acid [1], most of which is excreted by the kidneys [2]. Hyperuricemia is typically characterized as serum uric acid of at least 6mg/dl in women and at least 7mg/dl in men [3,4]. A significant consumption of red meat, seafood or alcohol is positively related to high risk of hyperuricemia [5]. This condition can lead to crystal precipitation in various tissues, including the kidneys, joints, and soft tissues [6]. It is widely recognized that uric acid leads to gout, but fewer people are aware that hyperuricemia may serve as a biomarker for cardiovascular risk.[7] Recent research has indicated that elevated serum uric acid levels are linked to the development of atrial fibrillation, hypertension, cardiovascular events [8,9,10], potentially through mechanisms involving endothelial dysfunction. In this review, we provide a summary of the current evidence regarding the relationship between uric acid and various cardiovascular diseases.

2. Potential pathophysiological mechanisms

The endothelium functions both as a barrier that separates the blood vessel lumen from the vessel wall and as an endocrine organ that secretes vasodilators (e.g. nitric oxide) and vasoconstrictors (e.g.

angiotensin II). It is essential in maintaining vascular homeostasis. A disparity between vasodilators and vasoconstrictors can result in endothelial dysfunction [11]. One of the key contributors to this dysfunction is oxidative stress. Although uric acid is often regarded as an antioxidant [12], it also exhibits several pro-oxidative mechanisms. These include reducing the production of nitric oxide, inhibiting vasodilatation [13], and promoting the formation of free radicals, which trigger inflammatory responses and impair endothelial function. Another harmful effect of uric acid on blood vessels is its stimulation of the renin-angiotensin system [14], which contributes to hypertrophy of vascular smooth muscle layer [15]. It contributes to atherosclerosis [11]. Despite these findings, it remains unclear whether uric acid is an independent casual risk factor for endothelial dysfunction. This uncertainty stems from the difficulty in isolating the effects of uric acid from those other closely associated risk factors, such as metabolic syndrome, hypertension, and alcohol consumption. Nevertheless, the mechanisms described above suggest potential links between uric acid and cardiovascular diseases.

3. Uric Acid and Cardiovascular Diseases

3.1. Uric Acid and Hypertension

Hyperuricemia is closely linked to hypertension, although the underlying mechanisms remains unclear. As previously mentioned, endothelial dysfunction significantly contributes to the development of elevated blood pressure. Several studies have demonstrated a notable association between hyperuricemia and the risk of developing hypertension [16,17,18]. In cross-sectional study in Japan, 7,484 adults were evaluated. Participants were categorized into groups according to their serum uric acid concentrations: group 1 (< 6 mg/dL), group 2 (6 - 6.9 mg/dL)), group 3 (7 - 7.9 mg/dL) and group 4 (≥ 8 mg/dL). Hypertension was characterized by blood pressure levels of ≥140/90 mm Hg or the use of high blood pressure treatment. Participants in the fourth group (≥ 8 mg/dL) had 1.89 higher risk of hypertension compared to those in the first group (< 6 mg/dL) [19]. In another study, 3329 participants without a history of hypertension, heart failure or gout had their serum uric acid levels measured at baseline. After a 4-year period, 458 individuals had developed hypertension, and 1201 had advanced to a higher stage of hypertension [19]. In both studies, the associations remained significant after adjusting for confounding variables such as age, sex, BMI, alcohol consumption, and kidney function.

A similar strong connection between hyperuricemia and elevated blood pressure has also been observed in pregnant women. A 2023 case control study investigated the link between pre-eclampsia and hyperuricemia. Pre-eclampsia was specified as blood pressure ≥ 140/90 mmHg and proteinuria ≥ 300mg/24h. The study involved 1365 women with pre-eclampsia and 1886 women with normal blood pressure. The results revealed that higher serum uric acid levels were associated with an increased risk of pre-eclampsia. Every increase of one standard deviation in serum uric acid level correlated with a 21%

increased risk [20].

Interestingly, the effect of uric acid-lowering treatment on blood pressure remains inconsistent across studies. A 2022 study evaluated patients aged 30-70 years with asymptomatic hyperuricemia and grade 1-2 hypertension, whose blood pressure was adequately controlled and who had not received prior urate-lowering treatment. Participants were randomized into two groups: one receiving allopurinol and the other serving as a control group without urate-lowering therapy. After six months of treatment, the allopurinol group showed significant reductions in office systolic and diastolic blood pressure compared to the control group [21]. In contrast, a 2021 study investigated 93 participants with baseline systolic blood pressure between 120 and 160 mmHg or diastolic blood pressure between 80 and 100 mmHg, none of whom had previously used urate-lowering therapy. Participants were randomized into two groups: one received allopurinol and the other received placebo for a duration of one month. The findings showed that systolic blood pressure did not change during either the allopurinol or placebo phases [22].

In conclusion, uric acid could be a contributing factor in the development of hypertension. However, effectiveness of uric acid-lowering treatment in managing blood pressure requires further research.

3.2. Uric Acid and Atrial Fibrillation

Atrial fibrillation remains a significant global health challenge. Recent studies have identified a link between hyperuricemia and an increased risk of atrial fibrillation, although underlying mechanism remains uncertain. Potential pathways may involve inflammation, endothelial dysfunction or cardiac remodeling. Oxidative stress has been demonstrated to trigger electrical remodeling in the atria, thereby promoting the re-entry mechanism [23]. In a prospective population-based cohort study in Norway, link between serum uric acid levels and future development of atrial fibrillation was investigated. A total of 6308 adults (both men and women) free of atrial fibrillation at baseline were followed for approximately 11 years. Baseline health information was collected, and at least 572 arrhythmias were identified during the follow-up period. Each one standard deviation increase in serum uric acid was linked with 17% increased risk of atrial fibrillation in men (95% CI, 1.02-1.36) and 40% increased risk in women (95% confidence intervals (CI), 1.14-1.72) [24]. Another study followed 123,238 patients in China over a period of approximately 8 years. Serum uric acid and additionally C-reactive protein (CRP) levels were measured. Participants in the highest quintile of serum uric acid had a 1.91-fold higher risk of atrial fibrillation compared to those in the lowest quintile (adjusted hazard ratio: 1.91; 95% CI, 1.32–2.76). Moreover, individuals with elevated levels of both serum uric acid and CRP had approximately 3-fold greater risk of atrial fibrillation compared to those with normal levels of both markers [25].

One study reported that the use of allopurinol was associated with a lower risk of developing atrial

fibrillation, particularly when taken for more than six months [26]. However, evidence in this area remains limited and warrants further investigation.

3.3. Uric acid and Heart Failure

Many cardiovascular diseases ultimately lead to heart failure. Hyperuricemia may influence this progression, although underlying mechanism is not clear. One study suggested that pro-inflammatory uric acid prevents insulin-stimulated glucose absorption, which results in myocardial insulin resistance. This, in turn, leads to impaired myocardial energy metabolism, affecting both diastolic and contractile functions of the heart [27].

Hyperuricemia is frequently observed in patients with heart failure. In 10-year prospective cohort study involving 54,606 participants, cumulative serum uric acid levels were assessed during successive evaluations. Individuals in the top quartile of cumulative serum uric acid had a significantly higher risk of developing heart failure compared to those in the first quartile (adjusted hazard ratio, 1.54; 95% confidence interval (CI), 1.29-1.84) [28]. Another study investigated impact of uric acid on the progression of heart failure with preserved ejection fraction in hypertensive individuals. A total of 1009 adults with hypertrophy of left ventricular and potential diastolic dysfunction were examined. Participants in the highest tertile of serum uric levels acid had a significantly increased risk of developing new-onset heart failure with preserved ejection fraction compared to those in the lowest tertile (HR: 1.761, 95% CI: 1.119-2.772, P = .015) [29]. Several meta-analyses have reported correlation between hyperuricemia and increased risk of heart failure. For example, a 2013 meta-analysis indicated that each 1 mg/dl rise in serum uric acid level was linked to a 19% higher risk of developing heart failure (HR 1.19, 95% CI 1.17–1.21), and a 4% increase in mortality risk among heart failure patients (HR 1.04, 95% CI 1.02–1.06) [30].

Research on effectiveness of uric acid-lowering therapy in improving heart failure outcomes has produced mixed results. A 2015 study reported that treatment with allopurinol in patients with led to improvements in NYHA functional class and reductions of NTproBNP levels [31]. However, EXACT-HF trial found that allopurinol did not improve clinical outcomes in patients with hyperuricemia and chronic heart failure. In this trial, 253 patients with symptomatic heart failure, left ventricular ejection fraction ≤40% and hyperuricemia were randomized to receive either allopurinol or placebo. After 24 weeks, no significant differences were observed in overall clinical status between two groups [32]. Moreover, a meta-analysis indicated that treatment with allopurinol was associated with a 24% increase in all-cause mortality risk among heart failure patients [33].

In conclusion hyperuricemia is associated with a poorer prognosis in heart failure. While some studies suggest that uric acid-lowering therapy may offer benefits, the majority of clinical trials indicate no

significant improvement in outcomes, and in some cases, even an increased risk of all-cause mortality.

3.4. Uric Acid and Coronary Artery Disease

Coronary artery disease remains the leading cause of mortality among cardiovascular conditions in developed countries. Hyperuricemia may represent an important risk factor in the development of atherosclerosis, potentially through mechanisms such as endothelial dysfunction, activation of renin-angiotensin system, and elevated blood pressure.

A cohort study involving 457,915 individuals without pre-existing cardiovascular diseases demonstrated that hyperuricemia notably raised the risk of coronary heart disease, particularly among adult women [34]. In another prospective cohort study, 422 patients with acute coronary syndrome and hypertension who had undergone percutaneous coronary intervention were followed for one year. In the findings of coronary angiography, multivessel coronary artery disease was found more frequently in the patients with hyperuricemia [35]. Another study reported a positive correlation between hyperuricemia and severity of coronary heart disease, as assessed by the SYNTAX score. A total of 705 patients undergoing coronary angiography were divided to four groups based on their SYNTAX score. Patients classified with severe coronary heart disease had the highest serum uric acid levels (6.5 ± 1.7 mg/dL) compared to those with normal coronary arteries (5.3 ± 1.5 mg/dL) [36]. Hyperuricemia may be linked to a higher risk of coronary heart disease mortality. This association was observed in meta-analysis involving 341,389 adults, which found that each 1 mg/dl increase in serum uric acid was linked to a 20% higher risk of death from coronary heart disease [37]. Similar results were reported in a separate meta-analysis of 958 410 individuals.[38] Interestingly, these studies also found that the effect of hyperuricemia on coronary heart disease mortality was more pronounced in women that in men [37,38]. To date, the role of uric acid-lowering therapy in preventing coronary heart disease has not been clearly established. In ALL-HEART trial, 5,721 patients with ischaemic heart disease were randomized into to two groups: one received allopurinol, and the other received standard care. Over a three-year period, 288 participants in the allopurinol group and 303 adults in the usual care group died, indicating the treatment with allopurinol did not significantly improve cardiovascular outcomes in this population [39].

4. Urate-lowering treatments

Currently, the most commonly uric acid lowering drugs are allopurinol and febuxostat. These drugs lower uric acid production, by blocking the enzyme xanthine oxidase. Their effects on cardiovascular diseases vary across studies. However, patients taking febuxostat have been shown to have a higher risk of both cardiovascular and all-cause mortality compared to those taking allopurinol [40]. As a result, febuxostat is not recommended as first-line uric acid lowering therapy.

Another class of uric acid lowering agents includes sodium glucose cotransporter 2 inhibitors (SGLT2), such as dapagliflozin. Their urate-lowering primarily mediated through modulation of two transporters: URAT1 and GLUT9. SGLT2 inhibitors modulate GLUT9 function and reduce URAT1 function, thereby increasing excretion of uric acid. Recent studies have confirmed that SGLT2 inhibitors not only lower serum uric acid levels but also reduce the risk of hyperuricemia-related complications and improve mortality outcomes in patients with cardiovascular diseases [41,42].

5. Conclusions

Hyperuricemia is associated with several cardiovascular diseases, including hypertension, atrial fibrillation, heart failure and coronary artery disease, and may serve as a useful marker for cardiovascular risk assessment. Although the exact pathophysiological mechanisms remain unclear, uric acid is thought to contribute to the development of endothelial dysfunction, which plays a key role in the progression of these conditions. The effect of uric acid-lowering therapy on the progression of cardiovascular diseases remains inconsistent across studies and requires further validation through larger-scale randomized controlled trials.

Disclosure

All authors contributed to the article.

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