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Cardiovascular Lesions and their Genetic Features in Patients with Gout

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Abstract: Uric acid (UA) is the final product of purine nucleotide metabolism in the human body. Hyperuricemia is an abnormally high level of uric acid in the blood, which can lead to arthritis and gout. The prevalence of hyperuricemia is growing worldwide. Epidemiological studies have shown that UA levels positively correlate with cardiovascular diseases (CVD), including hypertension, atherosclerosis, atrial fibrillation (AF), and heart failure (HF). Hyperuricemia contributes to the onset and progression of CVD by regulating molecular signals such as inflammatory responses, oxidative stress, insulin resistance/diabetes, endoplasmic reticulum stress, and endothelial dysfunction. Despite extensive research, the underlying molecular mechanisms remain unclear. It has been demonstrated that allopurinol, a xanthine oxidase (XO) inhibitor, improves cardiovascular outcomes in patients with HF, coronary artery disease (CAD), type 2 diabetes (T2D), and left ventricular hypertrophy (LVH). However, whether febuxostat, another XO inhibitor, can similarly improve cardiovascular outcomes remains controversial. Furthermore, it is uncertain whether urate-lowering therapy (ULT) can benefit patients with asymptomatic hyperuricemia. This review focuses on the latest cellular and molecular data regarding hyperuricemia-associated cardiovascular diseases and clinical data on the effectiveness of ULT in CVD patients.

Introduction

Uric acid (UA) is the final product of purine metabolism in higher animals, such as humans and primates. Under physiological conditions, the synthesis and excretion of UA in the body are balanced. When this balance is disrupted, it leads to hyperuricemia. Typically, a UA level above 7 mg/dL in men or above 6 mg/dL in women is considered hyperuricemia. However, Virdis et al. found that a threshold UA level of 4.7 mg/dL increases the risk of all-cause mortality, and 5.6 mg/dL increases the risk of cardiovascular mortality, both significantly lower than the clinical diagnostic criteria . With increasingly unhealthy lifestyles, the prevalence of hyperuricemia is rising, making it the "fourth largest" metabolic disorder after hypertension, hyperglycemia, and hyperlipidemia. Large-scale clinical studies on the relationship between serum UA (sUA) and cardiovascular diseases began with the Framingham Heart Study in the 1980s. Results from this study suggested that UA does not play a causal role in the development of coronary artery disease (CAD) or cardiovascular or all-cause mortality. However, recent epidemiological studies indicate that hyperuricemia is associated with hypertension, diabetes, atherosclerosis, chronic kidney disease (CKD), atrial fibrillation (AF), and the onset of cardiovascular events. Experimental studies have shown that hyperuricemia contributes to the onset and progression of cardiovascular diseases by regulating molecular signals such as inflammatory responses, oxidative stress, insulin resistance, endothelial dysfunction (Maruhashi et al., 2018), and endoplasmic reticulum stress.

An increasing number of clinical studies suggest that allopurinol can improve cardiovascular outcomes in patients with HF, CAD, T2D, and LVH. Compared to allopurinol, whether febuxostat improves

cardiovascular outcomes remains controversial. Furthermore, it is unclear whether ULT is beneficial for patients with asymptomatic hyperuricemia, as these patients are often associated with various risk factors (such as advanced age, CKD, CVD, obesity, metabolic syndrome, alcohol consumption, or smoking habits) but without overt disease. Moreover, UA acts as an effective antioxidant in cardiovascular and neurodegenerative diseases, complicating the relationship between UA and CVD. This review aims to explore the major mechanisms of hyperuricemia-associated CVD and the efficacy of ULT in CVD patients.

Methodology

Uric acid (UA) is the end product of dietary purine metabolism. Existing evidence suggests that UA plays a dual role in certain cardiovascular and cerebrovascular diseases. On one hand, UA exhibits antioxidant activity, capable of scavenging reactive oxygen species (ROS). As one of the primary endogenous antioxidants in the human body, UA accounts for up to 60% of plasma's antioxidant capacity, protecting cells from oxidative stress. The molecular mechanisms of UA's antioxidant effects include:

1. Reacting directly with hydroxyl radicals, peroxynitrite, nitric oxide, hydrogen peroxide, etc., to form stable intermediates;

2. Interacting with superoxide dismutase to eliminate oxygen radicals;

3. Chelating metal ions;

4. Inhibiting protein nitration, lipid peroxidation, and protein oxidation induced by peroxynitrite.

On the other hand, UA can stimulate oxidative activity within cells, potentially associated with ROS production. The prooxidant mechanisms of UA include:

1. Reducing nitric oxide production in arterial endothelial cells and inhibiting vasodilation

2. Inhibiting adiponectin synthesis in adipocytes;

3. Disrupting the tricarboxylic acid cycle and β-oxidation of fatty acids;

4. Activating the renin-angiotensin system, stimulating vascular smooth muscle proliferation and angiotensin II production;

5. Triggering chronic inflammatory responses.

The dual role of UA in antioxidant and prooxidant activity may be closely linked to xanthine oxidase (XO) activity in the bloodstream. Several studies have associated XO activity, a source of UA and ROS, with prooxidant and proinflammatory effects under pathological conditions. Significant progress has been made in recent years in understanding the relationship between UA and oxidative stress and its molecular mechanisms. Physiological concentrations of UA reduce oxidative stress-induced malondialdehyde and protein carbonyl levels, enhance superoxide dismutase (SOD) activity, and inhibit ROS formation in chicken embryo cardiomyocytes. The primary mechanism involves signaling pathways related to NF-E2-related factor 2 (Nrf2). In contrast, high concentrations of UA (1200 μM) inhibit Nrf2 signaling, increase malondialdehyde and protein carbonyl levels, and decrease SOD activity. Our research team has discovered that elevated UA levels suppress H9c2 cardiomyocyte viability and increase ROS production. Pretreatment with a ROS scavenger (N-acetyl-L-cysteine) and extracellular signal-regulated kinase (ERK) inhibitor (PD98059) reversed UA-induced cell viability reduction. Further studies indicate that elevated ROS levels induced by UA are closely associated with ERK/p38 activation and phosphatidylinositol-3-kinase (PI3K)/Akt inhibition.

Results

Uric acid (UA) has been a focal point in research due to its role in oxidative stress and its association with various inflammatory diseases. Atherosclerosis, a chronic immune-inflammatory cardiovascular disease, has been extensively linked to elevated intracellular UA concentrations. These concentrations promote the expression of inflammatory markers such as nuclear factor-κB (NF-κB), growth factors,

vasoconstrictive agents (Ang II, thromboxane, and endothelin-1), and chemokines through the activation of mitogen-activated protein kinases (MAPKs). Hyperuricemia also promotes macrophage polarization into M1/M2 phenotypes, which can be reversed with urate-lowering therapy (ULT). In obesity and cardiorenal diseases, UA tends to enhance the pro-inflammatory M1 response while inhibiting the anti-inflammatory M2 response. M1 macrophages secrete inflammatory cytokines, leading to insulin resistance and cardiac dysfunction. Conversely, M2 macrophages secrete interleukin-10 (IL-10), which inhibits cardiomyocyte hypertrophy and myocardial fibrosis. In a randomized controlled trial involving 106 patients with type 2 diabetes (T2D) and asymptomatic hyperuricemia, allopurinol effectively reduced serum UA (sUA) levels, improved insulin resistance, lowered high-sensitivity C-reactive protein (hs-CRP) levels, decreased carotid intima-media thickness, and mitigated atherosclerosis progression. The activation of inflammasomes plays a crucial role in various chronic inflammatory diseases. Recent studies indicate that sUA can effectively activate inflammatory processes in the cardiovascular system. Continuous inflammasome activation exacerbates inflammatory responses, damaging cardiovascular health. Research reported that UA activates NLRP3 inflammasomes and mitochondrial damage, leading to cellular injury in H9c2 cells. UA-induced activation of NLRP3/IL-1β inflammasomes occurs through NF-κB and mitochondrial ROS (mROS) signaling pathways. Suppression of UA levels through gene transfer of uricase or XO inhibitors has been shown to activate AMP-activated protein kinase (AMPK), thereby inhibiting atherosclerotic plaque formation.

Discussion and Conclusion

Atherosclerosis is the most common cardiovascular disease, with the highest morbidity and mortality rates. Possible mechanisms of UA-induced coronary artery disease (CAD) include:

1. Endothelial damage in large and microvessels: Uric acid deposits in vascular walls, stimulating vascular smooth muscle cell proliferation.

2. Activation of platelets, adhesion, and aggregation.

3. Hyperuricemia contributes to the production of inflammatory mediators (e.g., interleukins and C-reactive protein).

4. Increased reactive oxygen species (ROS) production leads to low-density lipoprotein (LDL) peroxidation, endothelial cell damage, vascular smooth muscle hyperplasia, and intimal thickening.

5. Direct oxidation of LDL by high UA levels.

Hyperuricemia is a potential risk factor for CAD, causing endothelial dysfunction through inflammation and oxidative stress, leading to unstable lipid plaques in coronary arteries and ultimately atherosclerosis. Thus, lowering UA levels is critical for CAD prevention and treatment.

Atrial fibrillation (AF) is the most common arrhythmia, with primary risk factors including advanced age, hypertension, obesity, diabetes, heart failure (HF), valvular disease, and myocardial infarction (MI). Clinical studies have confirmed a strong correlation between hyperuricemia and AF, particularly in postmenopausal women. UA-induced AF mechanisms involve oxidative stress, inflammation, and increased left atrial diameter, closely associated with AF onset and thromboembolism. Hyperuricemia also promotes Kv1.5 protein expression in atrial myocytes, affecting potassium channel function and shortening action potential duration. Heart failure (HF) is the terminal stage of most cardiovascular diseases and is strongly associated with hypertension, MI, AF, and valvular disease. Inflammation and oxidative stress are key factors in HF progression. Hyperuricemia contributes to myocardial insulin resistance, impairing glucose uptake, lipid metabolism, and myocardial energy homeostasis, affecting both diastolic and systolic functions. Two main urate-lowering therapy (ULT) classes are widely used in clinical practice:

1. XO inhibitors (e.g., allopurinol, febuxostat).

2. Urate excretion enhancers (e.g., benzbromarone, probenecid).

Clinical trials have shown ULT effectively reduces UA levels in hypertensive patients, but its impact on CAD, AF, and HF remains inconclusive. Febuxostat demonstrates higher efficacy and safety than allopurinol, but recent studies suggest febuxostat is associated with increased cardiovascular mortality compared to allopurinol. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors (e.g., dapagliflozin) effectively reduce UA levels and cardiovascular events, providing promising therapeutic options for hyperuricemia management in type 2 diabetes and cardiovascular disease patients.

Conclusion

The relationship between hyperuricemia and cardiovascular diseases is increasingly evident, driven by advancements in UA research. Hyperuricemia induces endothelial dysfunction, insulin resistance, and inflammation, contributing to hypertension, CAD, AF, and HF. Emerging treatments, including SGLT-2 inhibitors, offer potential therapeutic benefits, but further large-scale, randomized controlled trials are necessary to confirm these findings.

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