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Gout and Cardiovascular Diseases: Mechanisms, Risk Assessment and Impact of Therapy

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Abstract: Gout is closely associated with cardiovascular diseases (CVD), particularly atherosclerotic conditions, as well as other conditions such as heart failure, atrial fibrillation, and aortic valve stenosis. In addition to the common presence of vascular comorbidities in gout patients, gout itself is an independent risk factor for CVD. Events related to the disease and mortality are often attributed to this condition. The purpose of this review is to update current knowledge regarding several unclear areas in the spectrum of gout and CVD, focusing particularly on risk variations based on gender and origin, the potential deposition of monosodium urate (MSU) crystals in arterial walls as a pathogenic pathway, efforts to assess CVD risk in gout populations, and recent debates on the impact of gout therapy on CVD.

Keywords: gout; cardiovascular disease; cardiovascular risk; tophi; inflammation; hyperuricemia.

Introduction

Gout is a disease caused by the deposition of monosodium urate (MSU) crystals. Experts from the Gout, Hyperuricemia, and Crystal-Associated Disease Network (G-CAN) define gout as the presence of MSU crystal deposits accompanied by clinical manifestations such as flares, persistent arthritis, and/or tophi. However, the transition from asymptomatic hyperuricemia to gout can sometimes be unclear, particularly when MSU crystals have already formed. Clinically, gout is characterized by recurrent, self-limiting episodes of joint inflammation, and in prolonged untreated cases, subcutaneous tophi and/or chronic arthritis. Moreover, gout patients experience significant disability and a reduced quality of life, scoring worse on various scales, such as the Gout Assessment Questionnaire, the Health Assessment Questionnaire—Disease Index, or the Short Form-36, even during flare-free periods. Over the past decades, hospitalizations for gout have nearly doubled, and mortality rates among gout patients significantly exceed those of the general population, with a standardized mortality ratio of 2.21. There is a strong link between gout and cardiovascular diseases (CVD). Gout patients frequently suffer from multiple comorbidities where cardiovascular risk factors, such as hypertension, dyslipidemia, smoking, obesity, diabetes, and chronic kidney disease, play a significant role. Vascular diseases account for over half of deaths in gout patients; indeed, European data indicate cardiovascular mortality is six points higher than in the general population. Interestingly, gout and CVD exhibit a bidirectional effect: after a gout flare, the risk of cardiovascular events increases, especially in the short term. Additionally, the presence of gout worsens the patient's prognosis after a cardiovascular event or the success rates of coronary revascularization. Furthermore, gout flares often occur during hospitalizations for cardiovascular diseases. Studies also suggest links between gout and non-atherosclerotic cardiovascular diseases, such as atrial fibrillation, heart failure, and aortic valve stenosis. Combined data from the DATA-HF and DELIVER trials on dapagliflozin recently reported worsening heart failure outcomes in gout patients.

Methods

In addition to comorbidities, two main factors are likely responsible for the increased cardiovascular risk in gout patients: hyperuricemia and inflammation caused by MSU crystal deposition. Hyperuricemia has been associated with a prooxidant state, as the formation of uric acid by the enzyme xanthine oxidase (or xanthine dehydrogenase) leads to the production of prooxidant species, such as superoxide anions. Patients with hyperuricemia also exhibit higher levels of small oxidized low-density lipoprotein (LDL) cholesterol particles. These particles penetrate atheromatous plaques and exacerbate atherosclerosis. Moreover, studies in mouse models and clinical data suggest that hyperuricemia can cause arterial hypertension—at least in early life stages—likely through endothelial dysfunction. However, inflammation is the primary suspect linking gout to cardiovascular diseases, similar to other inflammatory diseases. MSU crystals can activate the NLRP3 inflammasome cascade, which in turn induces the synthesis and production of interleukin (IL)-1β and IL-18, key cytokines in crystal-induced inflammation. Interestingly, cholesterol crystals share the same inflammatory pathway in atheromatous plaques. Inflammation intensity varies significantly among gout patients. Apart from acute inflammation peaks (gout flares), persistent subclinical inflammation can occur during the intercritical stage, intensifying with higher crystal loads. However, this inflammation tends to decrease during urate-lowering therapy (ULT) or colchicine use. Beyond MSU crystal deposits, hyperuricemia itself plays a role in inflammation. Soluble urate can amplify inflammatory responses through multiple mechanisms in innate immune cells. Increased NLRP3 inflammasome expression has been observed in atheromatous plaques of hyperuricemic patients.

Results and Discussion

Given the variability in cardiovascular risk among individuals, predicting specific risks for gout patients is critical for tailoring clinical management, both in terms of cardiovascular health and gout treatment. This is particularly relevant for individuals without established cardiovascular diseases. To this end, several risk assessment tools have been developed to evaluate individual cardiovascular risk factors and predict the likelihood of cardiovascular events, including fatalities. Commonly used tools in primary care include the Framingham Heart Study (FHS) and the Systematic Coronary Risk Evaluation (SCORE), recently updated as SCORE2. However, no validation studies have been conducted for gout patients. Data from other inflammatory diseases, such as rheumatoid arthritis, suggest these tools may underestimate risks, leading to the development of specific risk calculators, such as the ERS-RA. Our group evaluated the effectiveness of FHS and SCORE in detecting subclinical carotid atherosclerosis. Both tools demonstrated moderate accuracy, with areas under the curve of 0.707 and 0.705, respectively. However, both lacked sufficient sensitivity (22.5% and 49.0%), despite good specificity results (89.3% and 80.4%). This suggests that high-risk cardiovascular patients might go undetected. Significant risk reclassification in gout patients can be achieved by categorizing them as having inflammatory arthritis under an adapted Dutch SCORE model. However, longitudinal data are needed to confirm these findings. It is essential to remember that risk assessment tools and carotid ultrasound are not applicable to high-risk individuals already suffering from cardiovascular diseases, complicated diabetes, and/or progressive kidney disease. Patients with tophaceous gout may fall into this category. Despite conflicting data regarding its association with subclinical atherosclerosis, subcutaneous tophi remain strong predictors of all-cause and cardiovascular mortality. Although MSU crystal deposition likely plays a leading role in gout-induced cardiovascular diseases through persistent subclinical inflammation and possibly arterial accumulation, urate-lowering therapy can reverse MSU deposits. Serum urate levels and the previous duration of gout are key factors in achieving complete removal of such deposits.

Conclusion

Over the past decade, significant advancements have improved our understanding of the relationship between gout and cardiovascular diseases (CVD). Gout is not merely a random symptom but an independent risk factor for CVD, associated with crystal-induced inflammation and hyperuricemia. Limited data suggest that gout has a similar impact on the cardiovascular system in both men and

women. Certain disease markers, such as subcutaneous tophi, indicating higher crystal loads, should be considered high-risk markers. Ultrasound and dual-energy computed tomography (DECT) have established connections between crystal deposits and atherosclerotic disease. These tools may prove useful as evaluative indicators in clinical practice. The goal of dissolving crystals should be guided by urate-lowering therapy, which could also provide cardiovascular benefits, despite conflicting data. Anti-inflammatory therapy may also contribute to addressing this issue, as evidenced by studies on cardiovascular patients. However, certain "gray areas" still need proper investigation through further research. Since CVD remains the leading cause of mortality among gout patients, addressing this issue through enhanced management strategies would significantly benefit patients and their families.

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