When gout goes to the heart: does gout equal a cardiovascular disease risk factor?

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Cardiovascular disease is among the leading causes of mortality in the world[1] and its prevalence is rising over time.[2] Inflammatory disorders such as rheumatoid arthritis and others are commonly associated with a higher risk and an earlier onset of cardiovascular disease. This increased risk may be mediated at least partially by non-traditional cardiovascular risk factors (inflammation and other disease activity factors), in addition to the traditional cardiovascular risk factors.[3 4]

In a study by Clarson *et al*,[5] the authors found that gout was a risk factor in women for incident coronary heart disease, any vascular event and peripheral vascular disease, but not cerebrovascular disease. The cardiovascular risk associated with gout was lower in men. The study used the Clinical Practice Research Database (CPRD) that includes 3.5 million people in the UK from general practices, stated by the authors to be representative of the general population with gout. The authors compared 8386 patients with gout with 39 766 non-gout patients. Despite the strengths of this study, including a large sample size, exclusion of patients with previously known heart disease and adjustment for important covariates, the study's findings must be interpreted in the light of two important limitations. First, the diagnoses of gout and most cardiac outcomes were not validated, but obtained from primary care records, which are likely to lead to some misclassification. Second, from an epidemiologic perspective, some people with disease may not seek care despite having access to healthcare due to either low/intermittent disease activity or personal health beliefs; also, there may be surveillance or detection bias because patients with gout may be more likely to visit primary care physicians than those who are healthy or do not have gout. Thus, the study's findings may be generally applicable to the UK population, but one may not have the same confidence in these findings as one would from a population-based cohort study.

IS GOUT A RISK FACTOR FOR INCIDENT HEART DISEASE?

One of the key metabolic abnormalities in gout, hyperuricaemia, is known to be associated with increased risk of cardiovascular disease, although causality has not been proved.[6–9] On the other hand, while there are some data suggesting that gout is a risk factor for incident heart disease, the overall literature in the area is somewhat mixed and debateable (table 1). The authors also cite it as the main reason for conducting the current study. The risk imparted by hyperuricaemia is of a small magnitude compared to other traditional cardiovascular risk factors, but it is significant. In addition, hyperuricaemia has also been shown to be a risk factor for peripheral vascular disease, another manifestation of atherosclerosis.[10 11] Some studies indicate that gout is an independent risk factor for incident cardiac disease (table 1).

WHY DO GOUT PATIENTS HAVE HIGHER RISK OF CARDIOVASCULAR DISEASE? THE CONTRIBUTIONS OF ENDOTHELIAL DYSFUNCTION AND SYSTEMIC INFLAMMATION

Gout, a metabolic disease associated with hyperuricaemia, leads to acute joint inflammation as part of a response to precipitation of urate crystals in the joint that commonly manifests as acute gout. Also, there is chronic inflammation around microtophi. Hyperuricaemia, a cardinal feature of gout, is associated with endothelial dysfunction, which may contribute to the risk of heart disease in patients with gout.[12] However, depending on the chemical microenvironment, uric acid may have antioxidant or pro-oxidant function.[13] In addition, uric acid likely contributes to the oxidation of lipoproteins within atherosclerotic plaque, thus contributing to the progression of lesions in coronary arteries.[14] Gout is associated with systemic inflammation. Markers of systemic inflammation, such as erythrocyte sedimentation rate and C reactive protein, are often elevated during acute gouty arthritis[15] and may even be raised in chronic active gouty arthritis.[16] Studies have linked systemic inflammation to the risk of heart disease in other similar chronic systemic inflammatory conditions, such as rheumatoid arthritis and lupus.[3 4 17 18]

A model for increased cardiovascular disease in gout is proposed, based on the current literature (figure 1). In the model, we allude to the mechanisms of cardiovascular disease, but due to lack of further evidence cannot propose what (hyperuricaemia vs acute inflammation vs chronic inflammation vs other yet unknown mechanism) exactly leads to that pathogenic step in cardiovascular risk (endothelial dysfunction, oxidation of low density lipoprotein (LDL), etc). Potential pathogenic mechanisms shown in patients with gout are either known (solid line) or suspected (dotted line). Similarly, the association of these mechanisms to the risk of heart disease is either known (solid line) or suspected (dotted line) in gout patients, or in general. For example, the association of hyperuricaemia (a cardinal feature of gout) with endothelial injury and acute and chronic inflammation is known, while its contribution to oxidation of LDL and elevation of other pro-atherogenic factors/mechanisms/pathways is suspected.

WHY DOES THE CARDIOVASCULAR RISK WITH GOUT DIFFER BY SEX?

Heart disease risk differs by sex in the general population. Women have a lower risk of heart disease compared to age-matched men in the pre-menopausal years—a protective effect of oestrogen. This benefit is lost in post-menopausal years and therefore the risk of heart disease in post-menopausal women catches up with men's risk of heart disease. Despite the differences in prevalence rates, the same risk factors for heart disease are key in both men and women—that is, smoking, diabetes, hypertension, hyperlipidaemia, and family history of heart disease. The early evidence from the current study and some others (table 1) indicates that the increase of heart disease risk might differ slightly by sex, the association being stronger in women compared to men. The absolute risk of any cardiovascular disease was 24.0/1000 person-years in men and 23.1/1000 person-years in women with gout, compared with 19.2 and 14.8/1000 person-years in men and women without gout, respectively. This shows that there is a difference in the risk of cardiovascular disease by sex in patients without gout and that this sex difference in cardiovascular disease risk is abolished in

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Table 1 Summary of large studies assessing the risk of cardiac disease in patients with gout

Study/country/ randomised vs cohort	Population	Odds/risk/hazard ratios (95% CI p value)	Covariates adjusted for in multivariable adjusted model
Krishnan *et al*[21]/USA/MRFIT	12 866 men in the MRFIT who were followed up for a mean of 6.5 years	Hyperuricaemia and MI: OR 1.11 (95% CI 1.08 to 1.15) Gout and MI: OR 1.26 (95% CI 1.14 to 1.40)	Age, diastolic blood pressure, total serum cholesterol, BMI, fasting blood glucose, smoking, creatinine, diuretic use, aspirin use, alcohol use, incident diabetes, family history of acute MI
Abbott *et al*[22]/USA/ Framingham	5209 subjects originally enrolled in the Framingham Study	Gout and coronary heart disease: RR 1.60 (95% CI 1.1 to 2.2) in men	Systolic blood pressure, total cholesterol, alcohol intake, body mass index, and diabetes
Gelber *et al*[23]/USA/two cohorts of black and white physicians	Prospective cohort studies of former medical students—371 black men in the Meharry Cohort Study and 1181 white men in the Johns Hopkins Precursors Study	Gout and incident CHD: RR 1.20 (95% CI 0.37 to 3.92) in Meharry men RR 0.66 (95% CI 0.24 to 1.79) in Johns Hopkins men	Known CHD risk factors
Janssens *et al*[24]/ Netherlands/case–control	Data were obtained from the Continuous Morbidity Registration (CMR), Nijmegen	Gout and incident CVS disease: RR 0.98 (95% CI 0.65 to 1.47)	Matched for age, sex and practice
De Vera *et al*[25]/British Columbia/population-based cohort	9642 gout patients and 48 210 controls, with no history of ischaemic heart disease	Gout in women: RR 1.39 (95% CI 1.20 to 1.61) for all AMI and RR 1.41 (95% CI 1.19 to 1.67) for non-fatal AMI Gout in men: RR 1.11 (95% CI 0.99 to 1.23) for all AMI and RR 1.11 (95% CI 0.98 to 1.25) for non-fatal AMI	Age, comorbidities (hypertension, diabetes, COPD, and hyperlipidaemia), Charlson comorbidity score and prescription drug use (non-steroidal anti-inflammatory drugs, aspirin, glucocorticoids, statins, anticoagulants, hormone replacement therapy and diuretics) as time-dependent covariates
Choi *et al*[26]/Health Professionals Follow-up Study/cohort	51 297 male participants of the Health Professionals Follow-Up Study with 12 year follow-up	In patients with no pre-existing CAD—Gout and total mortality: RR 1.28 (95% CI 1.15 to 1.41) Gout and CVD deaths: RR 1.38 (95% CI 1.15 to 1.66) Gout and fatal CHD: RR 1.55 (95% CI 1.24 to 1.93)	Age, hypertension, hypercholesterolaemia, diabetes mellitus, aspirin use, diuretic use, smoking, body mass index, alcohol intake, family history of MI, total energy intake, *trans* fat, dietary cholesterol, protein, linoleic fatty acid, and the ratio of polyunsaturated fat to saturated fat
Cohen *et al*[27]/US Renal Data System dialysis subjects	234 794 patients on dialysis in the US Renal Data System	Gout and mortality: HR 1.47 (95% CI 1.26 to 1.59)	Age, sex, diabetes, COPD, peripheral vascular disease, smoking, ischaemic heart disease, congestive heart failure, albumin, smoking
Kuo *et al*[28]/Chang Gung Memorial Hospital in Taiwan	61 527 subjects, with 1311 with gout	Gout and all-cause death: HR 1.46 (95% CI 1.12 to 1.91) Hyperuricaemia and all-cause death: HR 1.07 (95% CI 0.94 to 1.22)	Age, sex, component number of metabolic syndrome and proteinuria

AMI, acute myocardial infarction; BMI, body mass index, CAD, coronary artery disease; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; CVS, cardiovascular; MI, myocardial infarction; MRFIT, Multiple Risk Factor Intervention Trial; RR, relative risk.

men and women with gout. It is possible that systemic inflammation induced by gout in women, who otherwise have a lower prevalence of cardiac risk factors than age-matched men, is more atherogenic than that in men. Studies are needed to test whether there are sex-based differences in the pathogenesis of gout-associated heart disease.

DOES THIS MEAN GOUT PATIENTS SHOULD BE CAREFULLY SCREENED FOR CARDIOVASCULAR DISEASE RISK FACTORS?

Considering the ease of screening for risk factors, the suggestion is to screen gout patients older than 35 years (arbitrary—one may pick 40 years, for instance) with fasting lipid profile and glycated haemoglobin (HbA1c) monitoring, blood pressure measurement and current smoking status, and counsel/discuss with the patient if any risk factors are present. Patients should also be screened at regular intervals if their baseline is not normal and managed aggressively. Regardless of causality, the fact remains that patients with gout have a higher prevalence of numerous comorbidities, each of which can contribute to cardiovascular risk, and therefore require appropriate screening and management, as suggested by previous gout guidelines.[19 20] Since most gout patients receive care from primary care physicians, rather than rheumatologists, this is relatively easy. The only difference from the general population is an earlier age for screening, given the increased prevalence of cardiovascular disease risk factors in patients with gout and an increased associated risk. The goals are to prevent the onset of heart disease in patients with gout, and in those with early evidence of heart disease based on the workup with traditional markers and surrogates (such as serological and imaging biomarkers), institute treatments to improve outcomes.

WHAT SHOULD CHANGE IN PRIMARY CARE AND RHEUMATOLOGY PRACTICE BASED ON THESE DATA?

The end-organ damage from gout may not be limited only to the musculoskeletal system. Evidence is accumulating that the presence of gout matters for cardiac and vascular health, just as it does for joint health. It is to our advantage that a significant proportion of gout patients are managed by internists and cardiologists. A small, but significant, proportion of patients with gout may see cardiologists in addition to internists due to refractory pre-existing/concomitant cardiac conditions (coronary heart disease, congestive heart failure) and/or risk factors (hyperlipidaemia, hypertension, etc). However, in some of these cases, the cardiac or vascular disease has already manifested, meaning the window of opportunity may have been missed, and only secondary prevention (avoiding future myocardial infarction, etc) is possible. Real progress

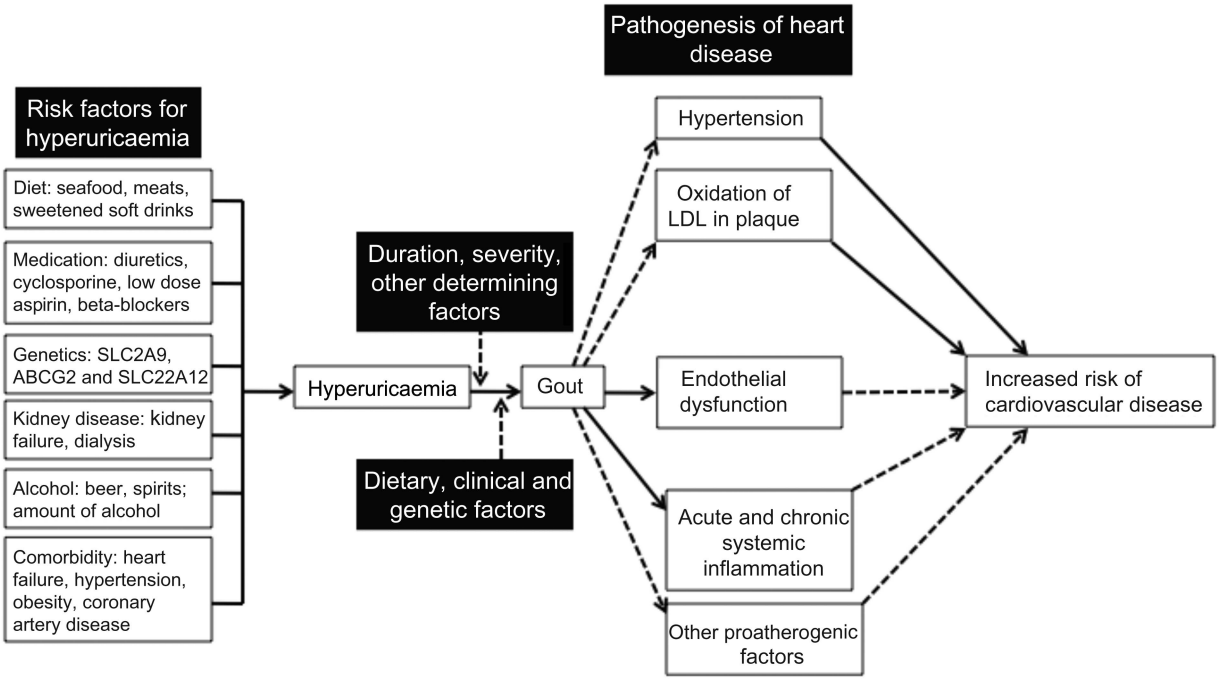

Figure 1 Potential pathogenic pathways for higher risk of cardiovascular disease in patients with gout. Solid lines indicate current evidence supporting the mechanism/pathway and dotted lines indicate potential mechanism/pathway, for which more evidence is needed. Several links from gout to the intermediate event (endothelial dysfunction, etc) may be through (mediated by) hyperuricaemia or non-hyperuricaemic pathways (eg, systemic inflammation).

in the care of gout patients can be measured by our ability to improve overall outcomes in gout patients including proactive recognition, early diagnosis, and optimisation of the treatment of heart disease—that is, primary prevention.

Primary prevention is always the goal of an epidemiologist, since the public health and individual level impact is much more substantial than secondary or tertiary prevention. It is very desirable to intervene early in high risk patients to modify traditional and non-traditional cardiac and vascular disease risk factors, before cardiac disease actually manifests. Mitigation of traditional cardiovascular disease risk factors such as hypertension is key to reducing this risk. Another approach might be to target and reduce systemic inflammation due to chronic gouty arthritis as well as acute gouty arthritis, by providing optimal urate-lowering (and anti-inflammatory) therapy, in order to additionally (potentially) prevent or delay the onset of cardiac disease in patients with gout. An effectiveness trial where the intervention targets systemic inflammation, with a sample size large enough to study cardiovascular disease or a surrogate outcome, is needed to test the following hypothesis: Does reduction in systemic inflammation in gout decrease the risk of cardiac disease and improve outcomes? Such a study will generate data that can lead to a change in the clinical practice for the treatment of gout. I anticipate that in the next decade aggressive management of gout will be key to implementing a 'healthier heart programme in gout'.

In summary, considerable data show an increased risk of cardiac disease in patients with gout, above and beyond that contributed by the traditional risk factors for heart disease. It is not known whether gout is an equivalent risk factor for cardiovascular disease to conditions such as diabetes or not. Future studies need to address this important question. At least two studies, including the current study, suggest that there may be an interaction with sex, meaning that the relative risk is different for men versus women. An implication of this new knowledge is that gout patients should be monitored and screened regularly for cardiovascular disease. Those with existing risk factors, such as hypertension, smoking, diabetes, hyperlipidaemia and others, are likely to be at high risk for cardiovascular disease. A comprehensive approach to treating uric acid appropriately to a target level, and to diagnosing and treating cardiac disease early, may lead to improved outcomes in patients with gout.

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