



Relation of serum uric acid to cardiovascular disease



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ABSTRACT

This review summarizes recent published literature on the association between serum uric acid and cardiovascular disease, a relationship which is complex and not fully elucidated. Uric acid may be a marker for risk, a causative agent in cardiovascular disease, or both. Various biologic factors can influence serum uric acid levels, and serum uric acid level itself is closely related to conditions such as hypertension, dyslipidemia, obesity, and impaired glucose metabolism, that contribute to cardiovascular disease pathophysiology. Serum uric acid levels have been found to be associated with adverse outcomes, including mortality, in the general population. In addition, serum uric acid is associated with increased risk for incident coronary heart disease, heart failure, and atrial fibrillation. In the setting of established systolic heart failure, serum uric acid is positively associated with disease severity and mortality risk. Whether targeting treatment based on uric acid levels might affect clinical outcomes is still being studied.

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1. Background

The association between serum uric acid (SUA) and cardiovascular (CV) disease has long been recognized. However, it has not been definitively established whether SUA is merely a marker for risk or a causative agent in CV disease, or whether treatment targeting SUA levels affects outcomes. SUA is closely related to conditions such as hypertension, dyslipidemia, obesity, impaired glucose metabolism, and metabolic syndrome, which contribute to CV disease pathophysiology [1,2]. Although many studies have found SUA to be independently associated with CV risk and events [3,4], there have also been compelling arguments made that the apparent association is primarily a function of SUA being strongly collinear with established CV risk factors [5,6]. Some of the variation in study results likely relates to differences in population characteristics and statistical methods, and the strength and independence of the association between SUA and CV disease pathophysiology and outcomes remain controversial. Therefore it is not known whether CV treatment should be targeted to lower SUA or tailored based on risk associated with SUA level. This review summarizes relevant studies examining the association between SUA and CV disease risk in the general population, and in the setting of specific CV disease states, as well as trials of SUA lowering and xanthine oxidase (XO) inhibition for treatment of CV disease.

2. Pathophysiology

Variations in SUA levels exist in association with various demographic factors such as race and sex, as well as CV comorbidities and medications (Table 1). In general, higher SUA levels are found in men versus women, with older age, higher blood pressure, increasing cholesterol level and creatinine, and higher body mass index [3,7,8]. Higher SUA levels are also associated with reported diuretic use, and intake of alcohol, meat and seafood [3,9,10]. Smoking does not appear to significantly influence SUA levels [3]. One study found lower SUA among African versus Caucasian men [11], although others have found higher SUA in black versus white persons [3]. There is also evidence for genetic influence of SUA levels in different racial/ethnic groups [12,13].

These associations are complex and confounded by causative relationships. Thiazide diuretics may induce hyperuricemia, and raise cholesterol and glucose levels [14]. Diuretic use may also be a marker for more severe hypertension, which is itself associated with elevated SUA. Hyperinsulinemia, a key feature of the metabolic syndrome, causes renal urate and sodium reabsorption, the latter of which may lead to hypertension [15]. In addition, some of the sex differences in SUA levels may be related to the presence of estrogen, which induces renal uric acid excretion [16], and SUA levels are indeed higher in women following menopause [5]. Some authors postulate that uric acid itself may be harmful, by inducing smooth muscle cell proliferation that leads to renal and vascular disease [17]. However, there is significant evidence that SUA is more of a marker for increased oxidative stress than a primary contributor to CV disease pathophysiology. Upregulation of the XO metabolic

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Table 1
Factors associated with higher serum uric acid levels.

- Male
- Elderly
- Higher blood pressure,
- High cholesterol level
- High creatinine
- Higher body mass index
- Diuretic use
- Intake of alcohol, meat and seafood
- Genetic influence in different racial/ethnic groups

pathway contributes to vasoconstriction and reduced myocardial function, increased oxidative stress and hyperuricemia [18].

3. General population

There have been inconsistent results of large population analyses of relationships of SUA to CV and all-cause mortality risk. Analysis of the community-based Framingham cohort, including 117,276 person-years of follow-up, found that SUA level was ultimately not associated with risk for incident coronary heart disease (CHD), CV death, or all-cause death. On initial analysis, it appeared that there was an increased risk associated with higher SUA among women, but in fully adjusted multivariate Cox models, this apparent risk was no longer significant. Once established risk factors such as blood pressure, diabetes, smoking, and diuretic treatment were added to the model, SUA was no longer significantly associated with risk [5]. A study of the British Regional Heart Study population found similar results. This study, including middle-aged 7735 men (average 16.8 year follow-up), found that SUA was strongly correlated with many CV risk factors and was positively associated with risk for fatal and non-fatal CHD events. However after full adjustment for potentially confounding clinical factors, this relationship was no longer significant. Although there was a trend toward significance in the subgroup of men with definite previous myocardial infarction, this relationship was not significant in the majority of the group (88% of the study population), who had no history of CHD [8].

In contrast, analysis of the First National Health and Nutrition Examination Survey (NHANES 1) Epidemiologic Follow-up Study (NHEFS) found that increased SUA levels were independently and significantly associated with risk of CV mortality among men and women, over an average 16.4 year follow-up. In this study, the HR for CV disease mortality was 1.09 (95% CI 1.02–1.18) for men and 1.26 (95% CI 1.16–1.36) for women, per 1 mg/dl increase in SUA [3]. The differing results of these two large studies have been attributed to differences in population characteristics. The NHANES population had more racial diversity and was on average slightly older than the Framingham population. In addition, all-cause and CV mortalities were significantly higher in the NHANES population, suggesting the presence of other important population differences [3]. Many other studies have generally found a positive association between SUA and CV and all-cause mortality, including large, community-based population studies [4,19,20].

4. Hypertension

SUA is positively associated with risk of incident hypertension [21]. Elevated SUA in the setting of hypertension may be related to renal involvement, leading to impaired uric acid excretion, and/or related to antihypertensive treatment. Hyperuricemia and hypertension may both result from the common pathway hyperinsulinemia due to insulin resistance, which increases urine sodium retention and decreases renal uric acid clearance. In the Systolic Hypertension in the Elderly (SHEP) study, increases in SUA below the median for the population (<0.06 mmol/L over 5 years) was associated with a lower risk for CHD events versus those with ≥0.06 mmol/L increase (HR 0.58, 95% CI 0.37–0.92) [22]. The Losartan Intervention for Endpoint reduction (LIFE) study found losartan

to be superior to atenolol in reducing CV events and mortality, among patients treated for hypertension [23]. Losartan is unique among angiotensin receptor blockers because it induces lowering of SUA [24]. ACE inhibitors and calcium channel blockers have mild uricosuric effects but do not significantly lower SUA, beta-blockers may have minor or neutral effects on SUA, and diuretics tend to increase SUA [25–27]. Although there was a lesser increase in SUA over time in the losartan treated group versus the atenolol group in the LIFE study, after adjusting for Framingham risk score baseline SUA was significantly associated with risk for CV events only among women (HR 1.013, 95% CI 1.00–1.025, $p = 0.046$) and not in men, or in the study population as a whole [23]. These findings suggest that, in the setting of hypertension, the prognostic effect of SUA is likely more related to the close association of SUA with traditional CV risk factors rather than a truly independent effect.

5. Coronary heart disease

SUA does not appear to be significantly associated with increased risk for incident CHD in the general population, but in groups at high risk for or with established CHD, the strength of the association found between SUA and mortality in various studies has been inconsistent. In the community-based Framingham population, SUA was associated with antihypertensive therapy, but after adjusting for multiple confounders, was not associated with development of CHD [1]. Among patients considered at high risk for CV disease (referred to Cleveland Clinic preventive cardiology clinic for evaluation and prevention of CHD), SUA was associated with an adjusted HR 1.26 (95% CI 1.15–1.38) risk for death, per 1 mg/dl increase [28]. In the Multiple Risk Factor Intervention Trial (MRFIT), which included 9105 men with an above-average risk for CHD, there was an increased risk for CHD death and death from any cause in persons with gout versus those without, over a 17 year follow-up period; however, there was only a weak association between hyperuricemia (defined as mean SUA over all 6 study visits of ≥7.0 mg/dl) and CV mortality [29]. In the British Regional Heart Study community-based population, there was only a non-significant trend toward association between SUA and risk for fatal and non-fatal CHD events among the subgroup of men with definite prior myocardial infarction [8]. After acute myocardial infarction, increasing SUA was significantly independently associated with 30-day and long term mortality; of note, SUA was closely correlated with Killip class [30], a measure of heart failure (HF) severity in the setting of acute myocardial infarction and a well-established and powerful prognostic indicator [31]. Other studies have also demonstrated increased risk for adverse outcomes associated with elevated SUA among patients with acute coronary syndromes as well [32].

6. Heart failure

SUA is associated with increased risk for incident HF, and with increased mortality risk in patients with existing systolic HF. In the community-based population of the Cardiovascular Health Study, SUA was associated with an increased risk for new-onset HF, with a HR 1.12 (95% CI 1.03–1.22) per 1 mg/dl increase in the population as a whole, and HR 1.30 (95% CI 1.05–1.60) among persons with hyperuricemia versus normals. In subgroup analysis, this relationship between SUA and incident HF remained significant only in groups in which hyperuricemia was likely related to increased XO activity leading to uric acid production rather than decreased renal excretion — specifically, groups without hypertension or renal disease, or being treated with thiazide diuretics [33]. In a similar analysis, it was found that SUA was associated with new-onset HF among patients without hyperinsulinemia, but not in those with hyperinsulinemia, despite higher SUA levels in the latter group. As XO activity is increased in the setting of insulin resistance and hyperinsulinemia, this finding suggests that the association may be due to increased XO activity rather than a direct effect of SUA [34].

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