Review
Gout

Hyperuricemia and cardiovascular disease: how strong is the evidence for a causal link?

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Abstract

An association between high levels of serum urate and cardiovascular disease has been proposed for many decades. However, it was only recently that compelling basic science data, small clinical trials, and epidemiological studies have provided support to the idea of a true causal effect. In this review we present recently published data that study the association between hyperuricemia and selected cardiovascular diseases, with a final conclusion about the possibility of this association being causal.

Introduction

Hyperuricemia and gout are closely related conditions that are prevalent worldwide [1,2]. The impact of these conditions on quality of life and work productivity has been well described, and for many years has been solely attributed to the burden caused by recurrent acute gout flares [3,4]. A possible link between hyperuricemia and cardiovascular disease has, however, been a debated clinical topic for many decades. Is hyperuricemia an independent cause of different types of cardiovascular disease?

In 1965 Sir Austin Bradford Hill presented considerations for epidemiological causation (Table 1) [5]. These considerations have limitations and exceptions but are nonetheless useful in trying to judge whether a given factor can make the leap from a simple association to being an independent causative factor. A more recent useful definition of an epidemiological cause is offered by Rothman and colleagues as 'an event, condition, or characteristic that preceded the disease onset and that, had the event, condition, or characteristic been different in a specified way, the disease either would not have occurred at all or would have occurred some time later' [6]. It is well established that hyperuricemia is a cause of gout. The association between hyperuricemia and cardiovascular disease was for many years only speculative, due to the absence of compelling epidemiological evidence suggesting hyperuricemia was independently linked with cardiovascular disease [7-9].

The objective of the present review is to present recently published animal, clinical, and epidemiological evidence that is contributing to a re-appraisal of the association between serum urate and cardiovascular diseases. From this evidence we will then judge the likelihood of a causative association between hyperuricemia and cardiovascular disease using the above-mentioned considerations for epidemiological causation. Readers with an interest in a comprehensive literature review on the topic could refer to the reviews published by Feig and colleagues [10], by Baker and colleagues [11], and by Edwards [12].

Serum urate and vascular effects in laboratory and animal studies

Using a rat animal model in which hyperuricemia was induced by the administration of the uricase inhibitor oxonic acid, a renal vascular disease that includes cortical vasoconstriction, afferent arteriolar swelling, and glomerular hypertension has been induced [13,14]. These physiological abnormalities were at least partially reversible by the administration of the nonreversible xanthine oxidase inhibitor febuxostat [15,16].

Several mechanisms have been postulated and are under investigation for explaining these perceived endothelial abnormalities induced by serum urate. Incubation of vascular smooth muscle cells with uric acid has been found to

CAD = coronary artery disease; CHD = coronary heart disease; CI = confidence interval; CKD = chronic kidney disease; IL = interleukin; IMT = intima-media thickness.

Table 1

Hill's viewpoints or considerations for epidemiological causation

Consideration	Explanation
Strength	Strong associations are intuitively considered more compelling. However, weak associations do not rule out causation.
Consistency	The association is found in different experiments, with different populations, and with varied circumstances.
Specificity	The most controversial consideration. A cause leading to a single effect (and *vice versa*) offers more support for the causation argument than one cause leading to multiple effects (and *vice versa*).
Temporality	The cause must happen before the effect.
Biologic gradient	A dose–response pattern is present, or incremental amounts of exposure should lead to corresponding increments in the effect.
Plausibility	The proposed association seems reasonable or probable as a cause. Most subjective consideration.
Coherence	A causative effect is not in conflict with current knowledge about the pathophysiology of the disease.
Experimental evidence	The effect can be reduced or altered by reducing or eliminating the proposed cause.
Analogy	Alternative explanations for the causative effect are evaluated and considered less likely than the one proposed.

stimulate proliferation, angiotensin II production, and oxidative stress. These changes were reversible by the addition of captopril or losartan, which suggested an effect mediated through the renin–angiotensin system [17]. Hemodynamic abnormalities found in the hyperuricemic rat model were reversed by the administration of a superoxide scavenger lending additional support to a link between elevated urate levels and damage induced by reactive-oxygen species (oxidative stress) [18].

Alterations in the expression of endothelin-1, which has been consistently associated with cardiovascular disease, have also been postulated as a potential mechanism of an association between hyperuricemia and cardiovascular conditions. Endothelin-1 exerts a powerful vasoconstrictive effect by binding to the receptors ET_A and ET_B in human vascular cells [19]. Human aortic smooth muscle cells exposed to different concentrations of urate experienced dose-dependent cell proliferation and phosphorylation-dependent endothelin-1 expression, along with an increased activity of NADPH oxidase (one mechanism of production of reactive oxygen species). Interestingly, those effects were reversible after treatment with antioxidants, such as *N*-acetylcysteine. The same group of investigators previously described the same mechanism of action for an increased production of endothelin-1 in cardiac fibroblasts [20]. How urate, known as an extracellular molecule, gains entry into vascular endothelial cells is still unknown but is possibly related to the demonstrated capacity of afferent renal arterioles to express URAT-1 [21]. This molecule is a urate-anion exchange transporter, expression of which had been described only in the renal tubular epithelium. The presence of URAT-1 in endothelial cells may allow for explanations of intracellular effects of urate in endothelial cells.

Serum urate and hypertension

Multiple population-based human studies have established a strong association between increasing levels of serum urate and subsequent development of hypertension (for a complete list, see [10]). This association has even been reported in subpopulations of individuals, such as those with rheumatoid arthritis in a recent cross-sectional prevalence study [22]. The degree to which epidemiological studies can control for potential confounders is variable, but most studies would examine the role of diuretics, dietary factors, and alcohol intake in the reported associations.

Interventional studies are few and occur in very selected groups of patients. Two recently published studies, however, have expanded the hypothesized role of hyperuricemia as a cause of hypertension by determining whether lowering serum urate improves hypertension in small numbers of patients.

Thirty adolescents (age 11 to 17 years) with stage 1 hypertension, treatment-naïve to antihypertensive medications, and with hyperuricemia (serum urate ≥6 mg/dl) were randomized to allopurinol or placebo in a crossover study [23]. With 4-week treatment phases and a 2-week washout period, the patients received 200 mg allopurinol or a matching placebo. During the allopurinol treatment phases, both the systolic and diastolic blood pressures were significantly reduced when compared with the respective pressures at the end of the placebo phases. These results were replicated when the pressures were measured by 24-hour ambulatory measurement. Twenty out of 30 patients normalized their blood pressures after treatment with allopurinol versus only one patient out of 30 upon treatment with placebo.

Supporting the hypothesis that the effect of urate may be mediated through stimulation of the renin–angiotensin system [17], the mean plasma renin activity was significantly decreased in patients after the allopurinol treatment phases [23]. These investigators hypothesize that early essential hypertension, as exemplified by these adolescent subjects, is both urate sensitive and salt insensitive. As the disease progresses with characteristic intimal and muscularis vascular wall changes, however, essential hypertension becomes urate insensitive and salt sensitive. These results were supported by the findings from another study that administrated 300 mg oral allopurinol daily to 48 patients with hyperuricemia (serum urate ≥7 mg/dl) for 12 weeks [24]. At the end of follow-up both systolic and diastolic blood pressures had small but significant reductions when compared with their pretreatment levels and with a group of normouricemic control individuals.

Serum urate and macrovascular disease

Evidence of an association between serum urate levels and surrogate markers of atherosclerosis, such as the carotid intima-media thickness (IMT), is starting to emerge. In a cross-sectional study of 234 healthy postmenopausal women there was a significant association between serum urate and IMT, independent of factors such as blood pressure, serum glucose, serum lipids, creatinine, smoking, and diuretic use [25]. Thirty patients with hypertension and hyperuricemia had their carotid IMT compared with that of 25 patients with hypertension but without hyperuricemia, and compared with 25 aged-matched healthy control individuals [26]. Patients with both hypertension and hyperuricemia had significantly greater carotid IMT than either control group, and in the overall population the carotid IMT was significantly associated with levels of serum urate. A significant association between serum urate and IMT persisted after multivariate adjustment in a group of 120 obese children [27].

Associations with macrovascular hard clinical endpoints associated with atherosclerosis have also been described. Eighty patients younger than 35 years of age clinically diagnosed with an acute myocardial infarction were divided among those patients who had coronary artery disease (CAD) by angiography ($n = 36$) and those patients with a normal angiography ($n = 44$) [28]. These groups were not different with respect to demographic characteristics or cardiac risk factors at baseline, but mean serum levels of urate (7.0 mg/dl among those with CAD vs. 4.9 mg/dl in those without CAD) were the main factor differentiating the two groups.

Other studies have found serum urate to be a prognostic factor after an acute or subacute macrovascular disease event. Higher levels of serum urate concentration were associated with late mortality, cardiac death, or nonfatal myocardial infarction in a retrospective cohort of 936 patients with CAD undergoing elective vascular surgery [29]. A review of two large independent studies in the United Kingdom (UK-TIA Aspirin, a randomized controlled trial; and Oxford TIA study, a prospective cohort) revealed that higher levels of serum urate conferred a greater risk for subsequent acute coronary events in women (but not men) after an acute ischemic stroke or a transient ischemic attack [30]. Finally, Lazzeri and colleagues found serum urate to be a significant and independent predictor of total mortality and inhospital mortality in a retrospective cohort of 466 patients admitted with ST-elevation myocardial infarction [31].

An association with stroke and surrogate markers for cerebrovascular disease has also become evident in recent years. Using T2 white-matter hyperintense signals in magnetic resonance imaging as a marker of brain ischemia, significantly greater frequencies of these T2 white-matter defects were found in association with higher levels of serum urate in 46 individuals (with serum urate concentrations >5.75 and >4.8 mg/dl for men and women, respectively) compared with 131 control individuals [32]. This association remained significant after adjustment for demographic and clinical potential confounders, and was likely to represent a true ischemic process in the studied population. As a clinical correlate, the same group of investigators also described an association between levels of serum urate and cognitive dysfunction in older adults [33].

To explore the potential for a therapeutic intervention, low (100 mg/day) and standard (300 mg/day) doses of allopurinol were administered to 50 patients with recent ischemic strokes that were enrolled in a double-blind, randomized, placebo-controlled study [34]. Allopurinol was well tolerated and significantly lowered levels of serum urate in the participants. The medication was associated with a significantly attenuated rise in the proinflammatory intracellular adhesion molecule-1, commonly observed after ischemic brain injuries. Allopurinol did not, however, reduce the levels of C-reactive protein or IL-6 as was expected.

Serum urate and cardiovascular mortality

In 1999 the Framingham Heart Study published the results of their ancillary study on the association of serum urate with cardiovascular disease and cardiovascular death. A total of 6,763 Framingham Study participants contributed a total of 117,376 person-years of follow-up. No significant associations were found in men or women after adjustment for cardiovascular risk factors and diuretic use. These results raised the question of an association of serum urate with cardiovascular disease and cardiovascular death probably confounded by other factors in the cardiovascular disease causal pathway [8].

Several large epidemiological studies investigating the association between serum urate levels and cardiovascular mortality have since been published. The majority had results in support of the association, but some of the studies

Table 2

Analysis of the association between hyperuricemia and cardiovascular disease using Hill's considerations

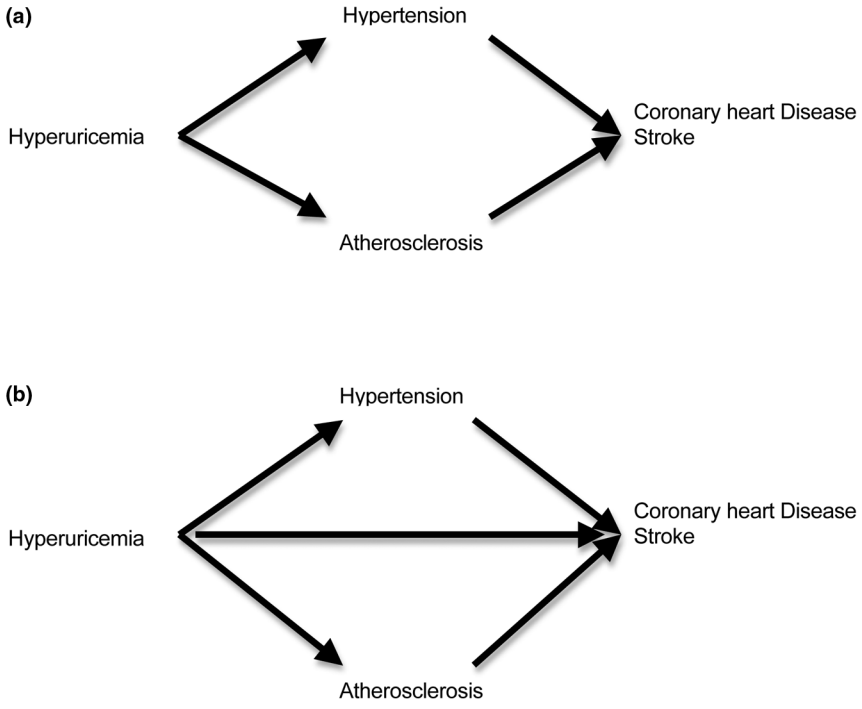
Consideration	Comment in view of current evidence
Strength	Associations with hypertension and cardiovascular mortality are not found to be particularly strong (relative risks and hazard ratios usually do not duplicate baseline risks) [10]. An exception is the strong association being recently described with chronic kidney disease [47].
Consistency	Limited evidence. Most associations have been described in North American and European Caucasian populations. Some large epidemiological studies are not in favor of the association.
Specificity	Not applicable for the most part. Cardiovascular diseases are complex and have multiple sufficient causative models, of which hyperuricemia could be considered an additional component cause. On the other hand, hyperuricemia is considered causative of other disease processes, like gout. The question of hyperuricemia being a causative factor for cardiovascular disease at all, or just a well-hidden confounder, has not been conclusively answered.
Temporality	Evidence from prospective studies has established a temporal relation between hyperuricemia and hypertension, stroke, cardiovascular mortality, and chronic kidney disease.
Biologic gradient	Large epidemiological studies in mortality of cardiovascular diseases and development of chronic kidney disease have established compelling dose-dependent relationships with population concentrations of serum urate [36-38,47].
Plausibility	In view of information provided by basic and animal models, plausibility is good.
Coherence	Remaining questions about its role in cardiovascular disease given its antioxidant properties [50]. Oxidative stress is considered a factor in atherosclerosis and cardiovascular disease, so can serum urate be a detrimental factor?
Experimental evidence	Experiments in animal models have added urate-lowering agents to revert renal vascular disease caused by hyperuricemia [15,51]. Initial experiences in treating hypertension, ischemic heart disease, and progression of chronic kidney disease have been published [23,24,34,48].
Analogy	Additional explanations, mainly that the relation between serum urate and cardiovascular diseases is not independent, have been progressive addressed. However, more evidence is needed.

reported negative results [11]. In 2000 a longitudinal follow-up analysis from individuals initially recruited into the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Survey was published, describing a significant independent association between higher concentrations of serum urate and cardiovascular mortality in both men and women [35]. In general, the associations were stronger for women than for men, and an association could not be found in two small subgroups of men: those taking diuretics and those with more than one cardiovascular risk factor. The National Health and Nutrition Examination Survey described the risk in a population with a better representation of non-Caucasians and a lower baseline cardiovascular risk than the one from the Framingham investigators, and its data could be considered more generalizable.

Other recent studies have provided additional valuable information by studying larger populations and specific groups of individuals. Data from the Vorarlberg Health Monitoring and Promotion Program in Austria were used to study the association between serum urate and mortality from coronary heart disease (CHD), from congestive heart failure, and from stroke in 83,683 healthy men followed for 20 years [36]. After adjustment for covariates, men with concentrations of serum urate >6.7 mg/dl had a significantly greater risk for death from congestive heart failure and from stroke, but not from CHD, when compared with those men in the lower category of serum urate concentration (<4.6 mg/dl). The hazard ratios for congestive heart failure and stroke were 1.51 (95% confidence interval (CI) = 1.03 to 2.22) and 1.59 (95% CI = 1.23 to 2.04), respectively. There were significant dose–response associations between concentrations of serum urate across categories and risk for death from CHD, from congestive heart failure, and from stroke in the study population.

The same group of investigators conducted a similar analysis in 28,613 women older than 50 years of age selected from the same population source and followed for 21 years [37]. In this population the hazard ratios for death from CHD, from congestive heart failure, and from stroke between women in the highest category (serum urate >5.4 mg/dl) versus the lower category (<3.7 mg/dl) were 1.35 (95% CI = 1.20 to 1.52), 1.58 (95% CI = 1.10 to 2.10), and 1.25 (95% CI = 1.01 to 1.56), respectively. Dose-dependent associations between serum urate concentrations across categories and hazard ratios for mortality were significant in all cases. This association was also studied in 3,098 individuals at high baseline risk for death from CHD [38]. Elevated serum urate was significantly associated with all-cause mortality, with each increase (mg/dl) conferring an excess risk for death of 26% (hazard ratio = 1.26, 95% CI = 1.15 to 1.38). In contrast, investigators studying 9,105 middle-aged men at high baseline risk for CHD from the Multiple Risk Factor Intervention Trial could not replicate a significant hazard ratio for CHD mortality, death from an acute myocardial infarction,

Figure 1



Theories on the causal association between hyperuricemia and selected cardiovascular diseases. Simple causal diagrams on the association between hyperuricemia and selected cardiovascular diseases. **(a)** Hyperuricemia has a direct effect on the development of hypertension and atherosclerosis, and an indirect effect on the development of coronary heart disease and stroke. **(b)** Besides the indirect effects described in (a), hyperuricemia has an independent effect on the development of coronary heart disease and stroke.

or death from any cardiovascular cause when comparing individuals with and without hyperuricemia [39]. A significant hazard for death from CHD among patients with gout, however, was reported (1.35, 95% CI = 1.06 to 1.72). Gender differences in the strength of these associations are not completely defined at this moment, although they seem to be more pronounced for women.

Reports of an association between levels of serum urate and cardiovascular mortality and all-cause mortality among patients with chronic kidney disease (CKD) have been discordant. Two independent groups of investigators have reported J-shaped or quadratic associations in patients with stage 5 CKD [40,41]. In these individuals increased hazard ratios for all-cause mortality were found among those in the lower and higher categories of serum urate, compared with those in the intermediate categories. In 461 patients with moderate CKD (average glomerular filtration rate 49 to 52 ml/minute) there was no significant difference in cardiovascular or all-cause mortality after multivariate adjustment, between those with and without hyperuricemia [42].

Serum urate and development of chronic kidney disease

Serum urate has been reported as an independent factor in the development of CKD and end-stage renal disease [43-46]. A recently published study has clarified the contribution of urate as an independent risk factor in the development of incident stage 3 CKD, defined as a calculated glomerular filtration rate ≤60 ml/min [47]. The study divided the participants (n = 21,475 healthy volunteers followed for a median period of time of 7 years) into three categories of serum urate levels: <7.0 mg/dl, 7.0 to 9.0 mg/dl, and >9.0 mg/dl. After adjustment for identified confounders, both higher categories of serum urate were associated with significant risks of developing stage 3 CKD (odds ratio = 1.74 (95% CI = 1.45 to 2.09) for the intermediate category of serum urate, odds ratio = 3.12 (95% CI = 2.29 to 4.25) for the higher category of serum urate). Additional data showed that the adjusted odds ratio increased linearly up to a level of serum urate approaching 7 mg/dl, after which the slope of the curve increased. This implied considerably greater risk for developing the outcome at serum urate levels >7 mg/dl. Previous pilot data that had explored the possibility of using allopurinol as a pre-emptive therapy to slow the progression of CKD reported success after 12 months of follow-up [48].

Reappraisal: hyperuricemia and cardiovascular diseases

Given the new information available we could attempt, using Hill's considerations for causation presented earlier, to re-

analyze the current status of the association between hyperuricemia and cardiovascular diseases (Table 2). Significant progress in the considerations about temporality, biological gradient, plausibility, and experimental evidence has been made. More evidence seems to be needed to support the considerations about consistency, analogy, and coherence. The associations between hyperuricemia and cardiovascular diseases have not been described to be as strong as associations of cardiovascular disease with smoking, hyperlipidemia, diabetes, and hypertension [49]. The association between hyperuricemia and cardiovascular diseases is not specific, but this one (specificity) is probably the most outdated of Hill's considerations.

We suggest a case for a true causal relationship between hyperuricemia and cardiovascular diseases. A word of caution is necessary here, however, as previous epidemiological associations have been proven wrong by well-controlled prospective studies. A possibility that needs to be thoroughly investigated is that known or unknown cardiovascular risk factors generate hyperuricemia, and that the latter is just an epiphenomenon with an apparent association with cardiovascular disease. An additional consideration is the possibility of a publication bias that over-represents study results in favor of the association.

Different kinds of studies are still needed to more precisely describe the nature of this association. More epidemiologic data are still needed in populations that have not been studied (for example, younger individuals). Pharmacoepidemiological surveillance to determine the impact of newly approved drugs for gout in cardiovascular outcomes will hopefully be required in the future by regulatory agencies. Carefully designed interventional studies involving larger and more representative groups of individuals should also be forthcoming.

Finally, if the link between hyperuricemia and cardiovascular disease proves true, what would be the nature of the causative association? Is serum urate a direct causative factor for cardiovascular disease? Or is serum urate a cause for factors that are in the causal pathway for cardiovascular disease (such as hypertension, atherosclerosis, metabolic syndrome)? Examples of simple causal diagrams reflecting theories around these questions can be seen in Figure 1.

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In conclusion, the paradigm of the causative association of hyperuricemia and cardiovascular diseases seems to have progressed from one of skepticism to one of increasing evidence of a true relationship.

Competing interests

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