Podagra, Uric Acid, and Cardiovascular Disease

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Hippocrates would not be surprised to read that persons with gout had higher mortality, and particularly cardiovascular-related mortality, than persons without gout.\(^1\) On the other hand, he might well have been bemused, nearly 2500 years after he described the syndrome, that this made news.

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The report assessed mortality for persons with prevalent gout at baseline and also for the combination of incident and prevalent cases. The actual incidence of gout was not reported. However, the comparison of deaths in the 2 analyses is puzzling. Total deaths among participants with gout at baseline for no CHD and CHD cases were 410 and 235, respectively. The inclusion of incident gout cases increased those figures to 451 and 456, respectively. If my understanding is correct, this means that a remarkable number of incident cases must have occurred over 10 years among the CHD group to generate the additional 221 deaths.

In any event, like Hippocrates, most present-day clinicians would be surprised that this is the first prospective study linking gout to mortality. As coronary artery disease has become more prevalent and its behavioral characteristics and risk factors identified, most clinicians, and probably the general public, have assumed that gout adversely affected survival. Choi and Curhan have now successfully exploited a large, well-conducted observational study to identify a hypothesis. Epidemiology, as William Kannel liked to remind us, is the attempt to prove guilt by association. The robust findings here are evidence that long-term cohort studies, despite their well-known limitations, can identify associations (new and old) that can then be tested experimentally.

The size and composition of the study group lend credibility to the conclusions drawn. However, information based on patient report does not have the same reliability as that directly obtained from patients and validated. Nevertheless, it seems reasonable to accept that the observed association is genuine and that the magnitude of that association is clinically important. Despite the absence of women and the narrow professional range of the men studied, there is little reason to quibble with the assertion that the biological impact of gout is probably similar in other groups as well.

Gout is a clinical syndrome whose pathophysiological construct is characterized by the deposition of urate crystals that provoke this common form of inflammatory arthritis. Wide geographic variation exists in the prevalence of gout. Approximately 5% of Maoris in New Zealand and \(\approx\)1% of adult Americans are affected. From the 1970s to 1990s, the annual incidence of gout in the United States has more than doubled from 20.2/100 000 to 45.9/100 000.\(^2\) Notably, the incidence of gout secondary to thiazide diuretic use did not increase during that time. Gout not only pains the patient but increase during that time. Gout not only pains the patient but also burdens the healthcare system in general and employers in particular. A diagnosis of gout nearly doubles ($6870 versus $3705) the healthcare expenditures for employed persons. Most of that is consumed by “circulatory system” conditions.\(^3\) Age is the most important risk factor for gout, and the condition is rare in premenopausal women. A variety of lifestyle-related factors, including obesity, alcohol consumption, high purine (primarily meat) intake, and medical
conditions such as hypertension, cardiovascular and renal disease, metabolic syndrome, and perhaps widening use of diuretics, together explain why the incidence and prevalence of gout are rising and probably will continue to rise in the near term.4

Uric acid, a measure not available in the Health Professionals Study, is the proximate element in the causal pathway that leads to gout. Gout is very rare in persons with a serum uric acid (SUA) level <6 to 7 (the solubility level of urate) and rises almost exponentially thereafter. Therefore, hyperuricemia is most likely the culprit responsible for increased mortality of persons with gout.

Thus, whereas the story here is ostensibly about gout, it inevitably raises the larger issue of whether hyperuricemia might be a modifiable risk factor for CVD. SUA is the sum of its production and excretion. Thus, diets rich in alcohol and meats (or other foods high in purines) and disease states with rapid cell turnover both produce hyperuricemia. Renal disease, by interfering with excretion, can lead to the same result. Hypertension, particularly when treated with thiazide diuretics, is also associated with elevated uric acid, as are obesity, diabetes mellitus, and the metabolic syndrome.2

The first specific indication that uric acid might be related to CVD was reported more than a half century ago when Gertler et al10 reported higher SUA levels in patients hospitalized with coronary artery disease than in those without.

Prospective cohort studies in general populations have primarily concluded that uric acid is associated with stroke and/or heart attack and that this association is independent of other cardiovascular risk factors, as well as elements of the metabolic syndrome with which uric acid levels are closely correlated. The one prominent dissenting conclusion was drawn from analysis of the Framingham Heart Study.6 Although SUA levels were correlated with CVD in women, after adjustment for other risk factors and diuretic use, the association was no longer significant in either men or women. By contrast, analysis of the National Health and Nutrition Examination Survey (NHANES) I Epidemiological Follow-up Study, 1971–1992, revealed a strong, independent association of uric acid and cardiovascular mortality.7 The relationship was stronger in women than in men, in blacks than in whites, and in persons older than 45 years. The incompatibility of the 2 studies is probably explained by population differences. The Framingham cohort was exclusively white and largely middle class, with better than average access to health care, whereas NHANES was a representative sample of the entire US population. The NHANES participants experienced far greater all-cause mortality and a near doubling of cardiovascular mortality compared with Framingham, convincing evidence that the 2 populations differed importantly. As it turns out, most prior studies have yielded results similar to NHANES.1,5,7–11 Thus, Framingham may only be an outlier among the large body of observational data now available.

In persons at high cardiovascular risk (hypertensive and diabetic subjects), the association of SUA with CVD events is even stronger than in the general population.11,12 Several careful studies have shown that SUA levels are more powerful predictors of mortality in heart failure than such conventional clinical parameters such as exercise capacity or kidney function.13,14

It is also interesting to note that, in persons with multiple sclerosis, a group characterized by hypouricemia, the incidence of CVD events appears to be lower than expected.15

Attempts to understand the causal pathway through which elevated uric acid might contribute to CVD have included studies to determine the relation of uric acid to target organ damage. The results have been mixed. In several, an independent association with left ventricular mass and other markers of target organ disease has been found.16–18 However, most recently, a clinic-based cross-sectional study of 580 generally healthy mildly hypertensive subjects failed to detect an independent association of SUA with either left ventricular mass, carotid abnormalities, or microalbuminuria.19 These results are consistent with several other similar studies. It should be noted, however, that only 8.3% of this Italian study population had hyperuricemia, which seems low for hypertensive patients. This may be due to the mild nature of their blood pressure elevation, youthfulness, and the absence of comorbidities such as obesity and diabetes commonly associated with hyperuricemia. In contrast to these results, others studies have found significant associations of uric acid and target organ damage.12

Several possible mechanisms through which uric acid might be responsible for vascular disease have been proposed. Johnson et al20,21 have shown, in a series of convincing animal experiments, that modest elevations of SUA can produce subtle glomerulotubular damage that, in turn, activates the renin-angiotensin system and elevates blood pressure, all of which were reversed by removal of the hyperuricemic stimulus. Hyperuricemia has also been shown to produce renovascular constriction and to correlate with activity of the renin-angiotensin system.22–24 Increased SUA has also been shown to play a role in endothelial dysfunction, produced either directly by increased SUA or through xanthine oxidase activity.25 Uric acid and xanthine oxidase are abundant in atherosclerotic plaques.26 The oxidative stress provoked by generation of oxygen free radicals, which reduce the availability of nitric oxide, decreases endothelial-regulated vascular relaxation.27 Free radicals occurring in the presence of hyperuricemia also stimulate lipid peroxidation, which might be responsible for increased carotid intima-media thickness.22,28 Other potential mechanisms by which hyperuricemia and/or elevated xanthine oxidase activity might produce vascular damage include increased platelet adhesiveness, smooth muscle cell proliferation, and stimulation of inflammatory responses. In short, a variety of mechanisms associated with hyperuricemia have been demonstrated that could reasonably be expected to contribute to CVD.29

However, neither epidemiological associations nor plausible biological mechanisms prove that a causal or, more importantly, a reversible link exists between SUA and disease outcomes. The most intriguing evidence to suggest that reversing hyperuricemia could prevent cardiovascular outcomes comes from studies of pharmacological intervention. Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) was a randomized trial of antihypertensive
therapy that compared losartan-based with atenolol-based treatment.\textsuperscript{30} Significant differences existed in the treatment levels of SUA between the experimental and comparison arms. The known uricosuric capacity of losartan, not present in atenolol or other angiotensin receptor blocking agents, resulted in subjects randomized to losartan having a significantly lower SUA. They also had reduced cardiovascular morbidity and mortality. Multivariable analysis suggested that the lower SUA might have accounted for as much as 29\% of the losartan advantage. These findings support the notion that reducing uric acid through increased excretion may have a vascular protective effect.

The alternate means of lowering SUA is to prevent its production. In that regard, allopurinol, by blocking xanthine oxidase, reduces uric acid production.\textsuperscript{31,32} Clinical studies have shown that allopurinol can improve endothelial function. In addition, allopurinol has been shown to decrease cardiovascular complications in patients undergoing coronary artery bypass surgery and improves cardiac function in patients with dilated cardiomyopathy and congestive heart failure.\textsuperscript{33,34} Thus, both reduced production and increased excretion have been shown capable of muting the adverse biological consequences associated with elevated SUA.

What, then, are the implications of the present study? The easy part is to endorse the recommendation by Choi and Curhan to aggressively control cardiovascular risk factors in patients with gout. Presumably, the same might apply to the vastly larger number of persons with hyperuricemia because most of those are likely to be either obese, hypertensive, or hyperlipidemic or to already have evidence of vascular disease. The more vexing problem is whether reduction of SUA by itself would be beneficial. A large body of epidemiological, clinical, and experimental data supports an association between hyperuricemia and CVD. The burden of stroke, heart disease, and kidney disease that persists even after control of all conventional cardiovascular risk factors is sufficient reason to judge current cardiovascular prevention efforts inadequate. Surely, identification of additional therapeutic targets whose treatment might reduce the burden of CVD would be welcome.

Unfortunately, present evidence does not justify a recommendation that hypouricemic therapy be instituted to achieve cardioprotection.\textsuperscript{29} On the other hand, no evidence exists that reducing hyperuricemia is harmful. Perhaps inclusion of a uricosuric antihypertensive agent should be considered when an angiotensin receptor blocker is otherwise thought to be appropriate therapy in a hyperuricemic patient. However, that begs the real question of whether hyperuricemia by itself is a risk factor that could be profitably reversed by either increased excretion, reduced production, or both. That will require a randomized clinical trial(s). I would argue that the available evidence now justifies such an investment. However, in the present climate, a trial designed solely to address the uric acid issue is unlikely to happen. On the other hand, randomized tests of other cardioprotective strategies will continue to be launched. Thus, it might be feasible to add a uric acid component to another more fundable study. The need for better CVD prevention should encourage the cardiovascular community to press for such an undertaking.

Disclosures

None.

References


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