Abstract

Gout is a chronic disease in which excessively high levels of serum urate (hyperuricemia) result in tissue depositions of sodium urate crystals and intermittent inflammatory attacks. Patients who have gout frequently experience a range of comorbidities, which complicates management and affects long-term prognosis. We review some of the more important of these comorbidities and consider the extent to which gout or hyperuricemia may be either a consequence or a cause of these related conditions. In addition, we briefly consider several neurological conditions in which the presence of gout or a high serum urate level may be associated with less disease, rather than more.

Gout is a chronic multisystem disease in which metabolic and excretory abnormalities, often compounded by excessive purine intake, result in hyperuricemia. In turn, hyperuricemia promotes the formation of monosodium urate crystals that induce inflammation (acute gouty arthritis) or deposit in tissues (tophaceous gout), or both. The complexity of gout is often underestimated, and recent studies suggest that the quality of gout care in the United States is frequently inadequate.1 One aspect of gout’s complexity is that patients with hyperuricemia or gout, or both, often experience high rates of comorbidities, raising management challenges.1,2 In a recent pilot survey of more than 500 patients with gout at our own VA hospital, we observed that the average gout patient endures approximately four comorbidities, and that as many as 5% to 10% of gout patients have seven or more comorbid conditions (MHP, DSG, RTK, unpublished observations). Indeed, the most common comorbidity seen in our cohort, hypertension, was present in more than three-quarters of our patients.

In considering the role of particular comorbidities in patients with gout, it is worth asking whether hyperuricemia and gout, or either, are a consequence of the comorbidity or a cause of the comorbidity, or whether the patient’s hyperuricemia-gout and their comorbidity derive from a common antecedent. In many cases, there is clear evidence that gout may be a consequence of a comorbidity. For example, gout occurs frequently in patients with chronic kidney disease, where the loss of glomerular filtration promotes hyperuricemia. In other cases, a common antecedent appears to connect the presence of gout with a particular comorbidity. For example, to the extent that hyperuricemia and cardiovascular disease may coexist in the same patient, obesity may be a common risk factor for both. On the other hand, it is important to consider the extent to which hyperuricemia or gout per se may contribute to the genesis of comorbidities; since both hyperuricemia and gout are treatable, their participation in causing other problems may suggest the potential for intervention. The issue of determining cause and effect in patients with gout can be a challenging one; in some cases, hyperuricemia or gout may be both a consequence of, and
a contributor to, a particular comorbidity. In this article, we briefly review some of the major comorbidities that occur in gout patients, with special consideration for the possibility that gout and hyperuricemia may represent modifiable risk factors for the comorbid condition in question.

**Hyperuricemia, Gout, and Hypertension**

As noted above, patients with gout frequently suffer hypertension, owing in part to the common antecedent of chronic kidney failure. However, evidence from both the clinic and the laboratory suggest that hyperuricemia, even in the absence of gout, may directly promote hypertension. For example, Ouppatham and colleagues conducted a study of more than 5500 members of the Thai Armed Forces, demonstrating that the presence of hyperuricemia predicts increased systolic and diastolic blood pressures. This effect was still observed after multivariate analysis to account for potentially confounding risk factors (including decreased renal function), leading the investigators to conclude that hyperuricemia independently raises the risk for hypertension. Such a conclusion is supported mechanistically by in vitro studies by Mazzali and coworkers (with RJ Johnson) and other investigators, who have demonstrated that soluble uric acid is a biologically active molecule that has potentially pro-hypertensive effects on both vascular endothelium and the kidney. For example, these investigators have shown that uric acid has the ability to 1. directly stimulate the renin-angiotensin system in the kidney; 2. inhibit the synthesis of vascular nitric oxide (NO); 3. induce renal abnormalities that can indirectly lead to hypertension, including inducing renal interstitial inflammation and tubular injury. Whether these in vitro effects are operative in the intact organism has been tested in several animal models. In one such model, rats were treated with oxonic acid (a uricase inhibitor) to approximate the human situation, in which our evolutionary loss of uricase resulted in increases in serum urate levels. In the presence of uricase inhibition, both serum urate levels and blood pressure were seen to rise. Moreover, both the increase in serum urate and the increase in blood pressure could be corrected by treatment with allopurinol, an agent that blocks uric acid generation by inhibiting xanthine oxidase. These results have more recently been reproduced using febuxostat, a more specific xanthine oxidase inhibitor.

To assess whether hyperuricemia might affect blood pressure in humans, Feig and coworkers recruited a group of adolescents with new onset essential hypertension and relative hyperuricemia. As a group, these individuals experienced a reduction of blood pressure towards or into normal range during treatment with 400 mg daily of allopurinol, concordant with urate lowering. This decrease in blood pressure was reversed on discontinuation of allopurinol. Whether this effect would be seen using other methods for lowering serum urate—and whether adults with hyperuricemia and long-established hypertension would respond similarly—remains to be determined. Moreover, while these studies suggest the ability of urate to influence vascular tone, they should be interpreted with some caution. For example, allopurinol is not entirely specific to xanthine oxidase alone, and lowering of urate also results in a number of related effects, including alterations of overall serum antioxidant levels, which could be the mechanism of action as opposed to urate lowering per se.

**Hyperuricemia and Chronic Kidney Disease**

It is well accepted that impaired renal function can decrease urate filtration and consequently hyperuricemia. In contrast, the question of whether hyperuricemia can promote kidney disease has been debated for years. As noted above, urate has a number of effects on kidney tissue in vitro and in animal models, including inducing tubular injury and interstitial inflammation. In rats that have been partially nephrectomized, administration of the uricase inhibitor oxonic acid results in increased proteinuria and glomerulosclerosis, whereas urate lowering using allopurinol reverses this effect. Perhaps the most dramatic demonstration of the capacity of urate to affect kidneys was carried out by Wu and associates, who, in 1994, generated a uricase knockout mouse. These mice rapidly developed severe urate deposition in the kidneys and renal failure, followed by death. Despite the fact that humans also completely lack uricase, the relevance of this model to human disease has been questioned, since the degree of urate deposition in the mice exceeds anything seen in human tissues. On the other hand, a large number of clinical studies do indeed suggest that hyperuricemia provides risk for renal disease, and, in many of these studies, the risk persists even after accounting for complicating factors. Moreover, several recent studies provide evidence that urate lowering using allopurinol may slow the progression of chronic kidney disease.

**Hyperuricemia, Gout, Insulin Resistance, and Obesity**

It is well known that individuals with metabolic syndrome have a higher incidence of gout, and, in this context, individuals with hyperuricemia may also have an increased incidence of insulin resistance. In one study, Yoo and colleagues showed that the incidence of insulin resistance in gout patients may be increased by as much as 35% over individuals without gout. Is this an incidental co-occurrence or is it possible that hyperuricemia may contribute to insulin resistance? The data in this regard rely mainly on in vitro and animal studies, and therefore conclusions must remain provisional. Sautin and coworkers reported on the stimulation of NADPH (nicotinamide adenine dinucleotidediphosphate) oxidase-dependent reactive oxygen species by uric acid. Stimulation with uric acid resulted in activation of MAP (mitogen-activated protein) kinases p38 and ERK1/2, a
Another issue that may confound the question of whether hyperuricemia as an independent player. Conditions will obscure, rather than confirm, any role for cardiovascular disease, correction for these “intermediate” if hyperuricemia induces conditions that, in turn, induce genesis of those conditions, as discussed above. Indeed, fails to account for the role that hyperuricemia plays in the vascular disease, however, since correcting for risk factors may underestimate the effect of hyperuricemia on cardiovascular disease for patients with hyperuricemia. Even this approach, which includes adjusting for confounding variables, the studies that included high-risk cohorts demonstrated a higher degree of risk for hyperuricemia than the studies that included the low-risk cohorts. Thus, it is possible that hyperuricemia is a more important cardiovascular risk factor in patients already at risk for cardiovascular disease.

Surprisingly, only a small number of studies have addressed the question of whether gout per se is a risk factor for cardiovascular disease, over and above that of hyperuricemia. Such a hypothesis is plausible to the extent that, in patients with gout, hyperuricemia has progressed to include either intermittent or chronic inflammation, both of which are assumed to be promoters of cardiovascular risk in other diseases such as lupus and rheumatoid arthritis. In an analysis of the MRFIT (Multiple Risk Factor Intervention Trial) investigation, Krishan and coworkers observed a modest increase for risk of myocardial infarction (MI) in patients with either hyperuricemia or gout, and patients with gout appeared to have an increased risk of MI relative to patients with hyperuricemia alone. However, these data were not analyzed to determine whether the increase in MI in the gout patients over the hyperuricemic ones was statistically significant.

**Beneficial Effects of Hyperuricemia and Gout?**

With all of the possible adverse effects of hyperuricemia and gout, it is worth asking whether there are any possible beneficial effects of these conditions. Uric acid itself may serve as an immune system stimulant, supporting the process of antigen presentation and even stimulating T cells in the absence of antigen. In addition, environmental biologists have posited that the loss of uricase in primates may have provided a survival advantage, either by raising antioxidant levels (urate being a potent antioxidant) or by helping maintain blood pressure in a salt-poor environment. However, these potential benefits of urate should be achievable at urate levels below those defined as hyperuricemic.

Interestingly, an evolving clinical literature suggests that hyperuricemia may be of benefit in several diseases of the central nervous system. For example, epidemiologic studies suggest that individuals with hyperuricemia may have a lower risk of Alzheimer’s disease than those with lower serum urate levels. In support of this observation, Irrizary and associates prospectively followed a group of individuals with baseline mild cognitive dementia. Over 36 months, individuals in the lowest serum urate quintile experienced significantly more progression of cognitive impairment, compared with individuals in the highest quintile. The

**Hyperuricemia, Gout, and Cardiovascular Risk**

Across many studies, hyperuricemia has been associated with cardiovascular disease. In many of these cases, however, investigators have regarded hyperuricemia as a byproduct of established risk factors, such as hypertension, renal insufficiency, insulin resistance, and obesity. Indeed, in some large population studies, multivariate analysis to account for these risk factors suggests that hyperuricemia is not an independent risk factor for gout.

However, the conclusion that hyperuricemia is not a risk factor may disregard a small but nonetheless independent effect of hyperuricemia seen across a larger number of studies. For example, in a review by Johnson and coworkers, every one of 14 large population studies identified hyperuricemia as a risk factor for cardiovascular disease, and 10 of the 14 studies favored hyperuricemia as an independent risk factor. Similarly, Wheeler and associates performed a meta-analysis of 15 studies, all of which included adjustments for established risk factors, and each demonstrated a modest overall increased relative risk for cardiovascular disease for patients with hyperuricemia. Even this approach may underestimate the effect of hyperuricemia on cardiovascular disease, however, since correcting for risk factors fails to account for the role that hyperuricemia plays in the genesis of those conditions, as discussed above. Indeed, if hyperuricemia induces conditions that, in turn, induce cardiovascular disease, correction for these “intermediate” conditions will obscure, rather than confirm, any role for hyperuricemia as an independent player.

Another issue that may confound the question of whether hyperuricemia is an independent risk factor for cardiac disease concerns the question of patient selection. Baker and colleagues examined 21 population studies on hyperuricemia and cardiovascular disease. They divided the studies into those including relatively healthy cohorts versus those including high-risk cohorts. Even after adjusting for confounding variables, the studies that included high-risk cohorts demonstrated a higher degree of risk for hyperuricemia than the studies that included the low-risk cohorts. Thus, it is possible that hyperuricemia is a more important cardiovascular risk factor in patients already at risk for cardiovascular disease.

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mechanism of this difference remains to be established, but might relate to the antioxidant rather than pro-inflammatory effects of urate. However, at least one study observed higher urate levels in patients with dementia, so this observation remains to be fully confirmed. A number of studies have documented that individuals with higher serum urate levels have a reduction (as much as 50%) in prevalence of Parkinson’s disease. Additional studies have confirmed a reduction in Parkinson’s risk in patients with gout versus those without gout. Whether this represents a cause and effect relationship between urate and Parkinson’s disease remains to be determined.

Finally, several studies have linked higher serum urate levels with a reduced risk of multiple sclerosis (MS). For example, Toncev and colleagues reported that individuals with lower serum urate levels had a reduction (as much as 50%) in prevalence of Parkinson’s disease. Additional studies have confirmed a reduction in Parkinson’s risk in patients with gout versus those without gout. Whether this represents a cause and effect relationship between urate and Parkinson’s disease remains to be determined.

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