Uric acid and cardiovascular risk considered: an update
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We present an up-to-date review of literature on the relationship of uric acid and kidney disease, cardiovascular disease and hypertension, with the recommendations that ensue.

Risk Factors and Prevention

Background

Hyperuricemia is defined as serum urate levels above 6.5 mg/dl, and it is well known that patients with higher levels are at increased risk of developing gout arthropathy, both acute arthritis or chronic tophaceus gout, uric acid urolithiasis and gouty nephropathy.

As urate-lowering agents are limited in number and effectiveness, allopurinol, a xanthine oxidase inhibitor, is the most commonly prescribed agent even with the fact that its utilization is limited due to its albeit uncommon, but potentially severe side effects (1). Febuxostat, a non–purine analogue inhibitor of xanthine oxidase, is used for the management of hyperuricemia in patients with gout, - as it has shown fewer adverse events in subjects with renal dysfunction when compared with allopurinol (2).
In the last decades there has been a reappraisal of the relationship between elevated urate serum levels and an increased risk of hypertension, other vascular risk factors and cardiovascular (CV) and renal disease (3-7).

1. Recent data concerning the effects of various antihypertensive drugs in the incidence of gout and, consequently, in cardiorenal disease, should be considered (8)
2. We need to develop recommendations regarding which should be the optimal management of patients with asymptomatic hyperuricemia and high-added CV risk.

I - Uric acid and kidney disease

Discovery of uric acid happened in the 1700's with the analysis of a bladder stone. Sir Archibald Edward Garrod first established a relationship between hyperuricemia and osteoarthritis only a century later, in the 1800's. Gout linked with chronic kidney disease was considered from the beginning. In fact, the condition defined as "gouty nephropathy" was originally attributed to the deposition of urate crystals in the tubules and renal interstitium heading to a local inflammatory reaction (9).

Data since has shown an association between increased uric acid levels and diminished renal blood flow, without variations in estimated glomerular filtration rate, and with increased renal and peripheral resistances. This would explain why the expression "gout nephropathy" has been abandoned and local crystal deposit have no longer been thought to be the reason for renal damage. Rather, kidney harm is believed to reflect prompt renovascular involvement owing to chronic hypertensive or age-related glomerulosclerosis (10), especially among subjects with essential hypertension. As a consequence and as of yet:

1. Although there is increasing evidence supporting hyperuricemia as a true risk factor of chronic kidney disease (11), there are still discrepancies regarding the contributing role of uric acid in the onset or worsening of kidney disease.
2. As of yet, there is still no agreement as to whether treating asymptomatic hyperuricemia in renal individuals with uric acid-lowering therapy will offer more renoprotection. Large prospective trials are needed to solve that.

II - Uric acid and cardiovascular disease

A relationship between hyperuricemia and CV disease has been established since the 1900's. Increased uric acid serum levels are a common finding in patients with high blood pressure, insulin resistance, obesity and CV disease. Furthermore, uric acid as a CV risk factor has been addressed in numerous prospective and cohort studies (12).
Nevertheless, debate arose from early times as to whether uric acid is an independent predictor of CV disease or not. It was later proven that both renal vasoconstriction and various CV drugs - principally renin-angiotenin system suppressors and insulin- were associated with reduced urate excretion, further studies showed that it was more accurate to regard hyperuricemia as a consequence of the existence of previously related CV risk factors (10). Yet, some theories were that increased uric acid levels would be good based on antioxidant properties (13), and positive outcomes on endothelial function were shown following the infusion of uric acid. On the other hand, an increase in blood pressure and increased salt sensitivity, stimulation of the renin-angioten system, and the development of insulin resistance, would all have been beneficial in certain situations, such as tissue injury and ischemia. This controversy caused uric acid to be no longer regarded as a true CV risk factor (14).
With increased awareness of the function of uric acid in cardiorenal disease, discussion has resurfaced in the last years. Epidemiological studies have revealed that uric acid concentrations predict the progression of chronic kidney disease (7) the development of stroke (5), and a recent meta-analysis reported that uric acid is associated with the presence of hypertension (3), diabetes (4), and metabolic syndrome (15). Relationship between coronary artery disease and uric acid, however, remains controversial. Another recent meta-analyses studying the relationship between uric acid and CHD showed that serum uric acid levels are not likely to be a main determinant of CHD and may not contribute significantly to the prediction of CHD in the general population (6). Nonetheless, the debate cannot be complete since conflicting information has put forward that uric acid could be a prognostic marker of CV events including myocardial infarction, heart failure, stroke and death (16). Finally, in patients with heart failure there is significant confirmation that elevated uric acid levels predict an increase in morbidity and mortality both in acute and chronic heart failure patients (17).
Recent evidence has emerged in parallel suggesting uric acid is an inflammatory factor that also plays a role in endothelial dysfunction. Thus, uric acid can induce proinflammatory changes in the adipocyte that are similar to those observed in the prediabetic subject (18). Finally, most of these trials suggested that uric acid's cardiorenal effects are due to its intracellular effects (1), unlike gout and stones. Therefore, practical conclusions regarding that relationship are that:

1. Treatment with xanthine oxidase inhibitors may be most effective in reducing intracellular uric acid because they will block intracellular production as well as decrease extracellular levels. Only a reduced number of studies have shown recently that the use of allopurinol may be beneficial in terms of CV outcomes (19). However, Because these data are few and the effects of allopurinol might not be limited to diminishing plasma uric acid levels, this point remains to be clarified with further studies.
2. The novel febuxostat, a non-purine analogue inhibitor of xanthine oxidase, has proven to be effective in reducing serum uric acid levels in patients with hyperuricemia and gout arthropathy (2), however still uncertain, is its potential for reducing the risk of developing CV disease.

III - Uric acid and hypertension

The relationship between uric acid and arterial hypertension was originally described in the early 60s, when prospective studies revealed that 26% of untreated hypertensive patients with normal renal function had elevated plasma uric acid levels. This outline increased to 58% for those receiving antihypertensive drugs, and it was principally high in those taking diuretics (70%)(20). As well, elevated uric acid levels in all subjects, both normotensive and hypertensive alike, have been related to a damaged vascular situation in the kidney usually due to atherosclerosis (10).
On the other hand, there is rising support that hyperuricemia, at least in certain populations, stimulates the onset of hypertension through the generation of an inflammatory cascade, where endothelial dysfunction, smooth muscle proliferation and development of renal afferent arteriolosclerosis appear.
Moreover, hypertension is one of the most common comorbidities of gout, affecting up to 74% of patients

with gout arthropathy, as described in the most recent estimations from the US National Health and Nutrition Examination Survey (2007-8). In addition, high blood pressure levels are independently associated with incident gout (3), due to the reduced renal blood flow added to both elevated renal and systemic vascular resistance, together with decreased renal excretion of urate.
Certain antihypertensive drugs can, as it is well known, modify the development of gout events in hypertensive patients, by increasing the levels of uric acid, - diuretics and betablockers especially. A recent case-control study evaluated, among a hypertensive cohort, the associations of different antihypertensive drugs with the risk of episodes of gout (8). The UK general practice database was used and 24 768 patients with newly diagnosed gout and 50 000 randomly controls among individuals between 20-79 years of age between the years 2000 and 2007 were included. The use of calcium channel blockers and losartan was associated with a significantly reduced risk of incident gout (relative risk 0.87, 95% confidence interval 0,82 to 0,93; 0,81, 0,70 to 0,94, respectively); the reduced urate levels due to an increased renal excretion of urate could explain this effect. On the other hand, diuretics, betablockers, angiotensin converting enzyme inhibitors, and non-losartan angiotensin receptor blockers were associated with a notably enlarged probability of gout. Interestingly, comparable outcomes were established in normotensive patients. Therefore, it has been suggested that:

1. Certain antihypertensive drugs could lead to a decrease in the high incidence of gout in hypertensive patients who are at high risk of developing gout. Similar results were described in subsequent analysis of the LIFE trial, where the higher decline in serum uric acid levels reached with a losartan based regimen when compared with the atenolol based one, explained 29% of the treatment effect on the primary composite end point of fatal and non-fatal myocardial infarction and stroke (21).
2. Likewise, the reduction in uric acid observed with losartan in the RENAAL study linked with the long term decrease in risk of renal injury compared with placebo, confirmed the renoprotective effects of losartan (22).

Conclusion:

Evidence regarding the relationship between high serum uric acid concentrations and hypertension and other cardiovascular risk factors is extensive. Furthermore, current data also suggest that hyperuricemia could increase the risk of developing renal and CV disease. Nevertheless, it is too early to make clinical recommendations in regard to the benefits of using xanthine oxidase inhibitor allopurinol or the novel febuxostat in patients with asymptomatic increased uric acid levels and high CV risk. Further studies are needed to assess the exact role of uric acid reduction in the progression of cardiorenal events.
Antihypertensive drugs can, however, modify the development of gout events in hypertensive patients, with losartan and calcium channel blockers having the greatest lowering effect on blood pressure because of their uricosuric properties.

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Notes to editor

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