Comorbidities in Patients with Crystal Diseases and Hyperuricemia

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KEYWORDS

• Crystal arthropathies • Comorbidities • Gout • Hyperuricemia
• Cardiovascular disease • Metabolic syndrome • Renal disease
• Calcium pyrophosphate arthropathy

KEY POINTS

- Recent evidence has shown that asymptomatic hyperuricemia, as well as hyperuricemia in patients with gout, plays a significant role in the development of cardiovascular comorbidities.
- In addition to an already proven association between hypertension and hyperuricemia, interventional trials are showing a positive effect of urate-lowering therapy in early stages of hypertension in young individuals.
- An association between hyperuricemia and other cardiovascular diseases such as coronary heart disease, congestive heart failure, and stroke is still not clear.

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- A link between hyperuricemia, insulin resistance, and the metabolic syndrome has been shown by fructose-fed animal models and may explain the association between 2 overlapping and increasing diseases.
- Hyperuricemia is associated with an increased risk of chronic kidney disease, but the use of urate-lowering therapy in these patients is still not clear.
- Evidence regarding calcium pyrophosphate arthropathy and associated comorbidities is still scarce and not conclusive.

Crystal arthropathies are among the most common cause of arthritis worldwide. Of these arthropathies, gout represents the highest known burden of crystal-induced arthritis and is likely the most common type of inflammatory arthritis in adults in the United States.[1,2] Calcium pyrophosphate arthropathies, initially described as pseudogout,[3] and other calcium crystal arthropathies are less commonly recognized than gout. Although initially observed only as a painful inflammatory arthropathy, in recent years, more evidence has been building up the case for an association between gout and hyperuricemia and important cardiovascular-metabolic conditions.[4–8] This article presents an updated review of the evidence for these associations, as well as comorbidities associated with calcium crystal arthropathies.

COMORBIDITIES ASSOCIATED WITH HYPERURICEMIA AND GOUT

Hyperuricemia, defined as a serum urate (SU) concentration higher than the point of saturation of 6.8 mg/dL or more,[9] is the most common biochemical abnormality associated with the development of gout, but it is not a sufficient causative factor. Individuals in whom SU concentrations are increased above saturation levels but have not developed clinical manifestations of gout are considered to have asymptomatic hyperuricemia. Data from the US National Health and Nutrition Examination Survey (NHANES) 2007–2008 study estimated a gout prevalence of 3.9% (5.9% for men; 2.0% for women), but a higher hyperuricemia prevalence of 21.4% (21.2% for men; 21.6% for women).[5] In the following sections, the experimental and epidemiologic evidence linking gout and various comorbidities and their complex interrelationships is summarized.

Cardiovascular Disease

Urate and the endothelium: laboratory and animal studies

In vitro studies that used urate concentrations similar to in vivo levels have shown several potential vascular effects. These effects include suppression of nitric oxide (NO) levels,[10,11] increased platelet-derived growth factor expression, local thromboxane production, and cyclooxygenase 2 stimulation, as well as induction of endothelial proliferation, angiotensin II production, and increased markers of oxidative stress.[12–14] The key role of the renin-angiotensin system (RAS) was proved by the reversibility of these effects by adding captopril or losartan.[13] Other significant in vitro observations include the increased production of endothelin 1, a powerful vasoconstrictor, on human aortic smooth muscle cells and cardiac fibroblasts under different urate concentrations.[15,16] All of these effects are facilitated by the entry of urate to vascular smooth muscle cells via the urate anion transporter 1 (URAT-1), an integral membrane protein that serves as a urate transporter and was initially described in afferent renal arterioles.[17]