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COMORBIDITIES IN PATIENTS WITH CRYSTAL DISEASES AND HYPERURICEMIA

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Summary

Crystal arthropathies are among the most common causes of painful inflammatory arthritis. Gout, the most common example, has been associated with cardiovascular and renal disease. In the last years, evidence on these associations and those involving other comorbidities, such as the metabolic syndrome, have emerged and established the importance of asymptomatic hyperuricemia. This review article presents an update on evidence, both experimental and clinical, describing associations between hyperuricemia, gout, and several comorbidities. Causality on calcium pyrophosphate arthropathy and associated comorbidities is also briefly reviewed.

Keywords

crystal arthropathies; comorbidities; gout; hyperuricemia; cardiovascular disease; metabolic syndrome; renal disease; calcium pyrophosphate arthropathy

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Crystal arthropathies are amongst the most common cause of arthritis worldwide. Of these, 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 by McCarty and colleagues, and other calcium crystal arthropathies are less commonly recognized than gout.[3] Although initially observed only as a painful inflammatory arthropathy, in the past 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 will present an updated review of the evidence on 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 above the point of saturation of 6.8 milligrams per deciliter (mg/dL) or more,[9] is the most common biochemical abnormality associated with the development of gout, but is not a sufficient causative factor. Individuals in whom SU concentrations are elevated above saturation levels but have not developed clinical manifestations of gout are considered to have asymptomatic hyperuricemia. Data from the Unites States 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 sections below, we summarize the experimental and epidemiological evidence linking gout and various comorbidities and their complex inter-relationships.

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 include suppression of nitric oxide (NO) levels,[10,11] increased platelet-derived growth factor expression, local thromboxane production, 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 proven 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]

In vivo animal models have also supported data from in vitro studies. Hyperuricemia was induced in rats through the administration of oxonic acid, a uricase inhibitor, which led to renal vascular disease characterized by cortical vasoconstriction, afferent arteriolar swelling, and glomerular hypertension. [18,19] Partial attenuation of these abnormalities was obtained through the administration of the non-reversible xanthine oxidase inhibitor, febuxostat.[20,21] Other animal models supported these observations and have also shown that although early

hypertension can be corrected with SU reduction, after prolonged hyperuricemia urate reduction doesn't translate into control of blood pressure and avoidance of arteriolar thickening. Prolonged hyperuricemia results in an irreversible sodium-sensitive urate-insensitive hypertension.[14,22] These observations have pointed to a two stage model, with an early hypertension mediated by increased renal renin activity and reduction of circulating plasma nitrates, and a later irreversible phase secondary to an altered intrarenal vascular architecture [see Figure 1].[23]

Hypertension—In 1999, a study of the Framingham cohort reported an association between hyperuricemia and hypertension, which has been confirmed by other epidemiological studies in different populations.[24–31] Recently, the National Health and Nutrition Examination Survey (NHANES) 2007–2008, analyzed the prevalence of gout, hyperuricemia and comorbidities in non-institutionalized adults. Hypertension was present in 74% with gout, and in 47% with hyperuricemia (defined as a SU >7.0mg/dl for men and >5.7 mg/dl for women) but no history of gout, in comparison to a population-estimated prevalence of 24% among normouricemic patients. Prevalence amongst gout population with and without hyperuricemia was 77.7% and 70.8% respectively, higher in comparison to individuals with asymptomatic hyperuricemia. The prevalence of hypertension was significantly higher amongst individuals in the higher SU category (SU ≥ 10mg/dL) in comparison to those in the lowest SU category (SU <4 md/dL).[5]

A meta-analysis that pooled 11 studies showed a significantly increased risk ratio for incident hypertension of 1.41 (95% CI 1.23–1.58) among individuals with hyperuricemia, after adjusting for traditional risk factors, including age, BMI, alcohol and tobacco use. This risk appeared more pronounced in younger individuals and women. An increased pooled relative risk for incident hypertension of 1.13 (95% CI 1.06–1.20) per each mg/dL increase in SU was calculated from six studies[32]. Another meta-analysis including 8 prospective studies also reported an increased risk, pooled RR 1.55 (95% CI 1.32–1.82), for hypertension when comparing the highest quartile to the lowest one of SU. However, the analysis presented showed significant heterogeneity ($p<0.05$).[33]

Most interventional studies come from adolescent or pediatric population. A relationship between primary hypertension and high SU levels has been observed in even at concentrations below the supersaturarion value of 6.8 mg/dL, and one study has reported elevated SU levels (>5.5 mg/dL) in up to 90% in children with primary hypertension.[34–36] A small randomized, controlled, crossover trial of 30 treatment-naïve adolescents (11–17 years old) with stage I hypertension and hyperuricemia, randomized individuals to receiving oral allopurinol 200 mg daily or placebo undergo a washout period and then crossover intervention arm. After treatment, 20 of 30 participants achieved normal blood pressures in comparison to one participant taking placebo.[37] A randomized, double-blind, placebo-controlled study compared allopurinol with probenecid, in pre-hypertensive obese adolescents. Both treatment arms had a significant decrease in SU, and led to a 10.2 and 9.0 mm Hg reduction in systolic and diastolic blood pressure, respectively. These results suggested that reduction in blood pressure was related to the urate lowering effect and not to the decreased xanthine oxidase activity.[38] A similar study with a small sample of hyperuricemic adults receiving allopurinol 300mg daily also supported the blood pressure

reduction with urate lowering therapy (ULT).[39] Despite these encouraging results, a recent Cochrane review on pharmacotherapy for hyperuricemia and the reduction of blood pressure concluded that evidence is still insufficient to recommend ULT.[40]

Atherosclerosis, coronary heart disease and peripheral arterial disease— Several mechanisms such as maintenance of a pro-inflammatory state, promoting a proliferative response in vascular smooth muscle cells, and alterations in the renin-angiotensin system and promotion of hypertensive state may explain the link between urate concentrations and cardiovascular disease. Contributing to this association, elevated levels of monosodium urate have also been observed in atherosclerotic plaques.[41] Carotid intima-media thickness (IMT), regarded as a surrogate marker for atherosclerosis, has been shown to have a significant association with SU levels in cohort of healthy postmenopausal women, and also in a different cohort of hypertensive individuals with and without hyperuricemia.[42,43] Another study also reported a dose response relation between SU and carotid atherosclerotic plaques in men with and without cardiovascular risk factors.[44] However, the same group didn't find any association between the levels of SU and coronary artery calcification (CAC).[45] The associations between serum urate, CAC, and IMT were re-evaluated in an analysis of 5115 young adults aged 18–30 years at followed for 25 years. Using CAC and carotid IMT as markers of subclinical atherosclerosis, the investigators reported increased risks for CAC progression from years 15 to 25 with respect to baseline SU. For carotid IMT, SU at year 15 significantly predicted greater IMT at year 20, but this association only remained significant in men after adjusting for BMI. Greater increments in SU concentrations from years 0 to 15 were associated with higher risks of CAC progression and IMT.[46] These findings supported a role for serum urate as a potential biomarker of subclinical atherosclerosis in young adults.

Urate- induced endothelial dysfunction secondary to reduced NO production, actually precedes plaque formation[47] and may play a more direct role [see Figure 2]. A recent review and meta-analysis of the use of xanthine oxidase inhibitors for the treatment of cardiovascular disease, evaluated three outcome parameters (brachial artery flow mediated dilation, forearm blood flow responses to acetylcholine infusion and circulating markers of oxidative stress) and showed a significant improvement in each of them in patients with, or at risk of, cardiovascular disease.[48] However, data on this aspect is still not conclusive.

Since the Framingham Heart Study in 1999 failed to identify a significant association between SU, cardiovascular disease, and cardiovascular death;[49] several other population studies have presented contradictory evidence. An NHANES 2007–2008 analysis reported a 14% prevalence of myocardial infarction among individuals with gout, with an age- and sex-adjusted OR of 2.68 (1.45 for men; 6.86 for women) compared to non-gout individuals. Prevalence of myocardial infarction in individuals with hyperuricemia was 5.7%, with an OR of 1.21 in comparison to normouricemic individuals. Myocardial infarction prevalence was significantly higher in hyperuricemic or normouricemic individuals with gout (11.6% and 14.1% respectively), in comparison to hyperuricemic individuals with no diagnosis of gout (5.7%).[5] Other studies also support an increased risk of coronary heart disease (CHD) in women with gout.[50] Recently, a population-based study of a Taiwanese cohort also

reported gout as an independent risk factor for myocardial infarction, and stated that this risk was greater in younger individuals without cardiovascular risk factors.[51]

An initial meta-analysis on the subject reported a 13% increased risk (RR 1.13 95% CI 1.07–1.20) of CHD among those in the top tertile of SU levels compared to those in the lowest tertile.[52] A more recent meta-analysis of 26 studies with 402,997 adults reported a modest but significant increased risk of CHD incidence and mortality on hyperuricemic individuals, 1.09 (95% CI 1.03–1.16) and 1.16 (95% CI 1.05–1.19) respectively, even after adjusting for traditional risk factors. A non-significant increased CHD mortality RR of 1.12 for was reported for each 1mg/dL SU increase, with only the women subgroup analysis having a statistically significant but modest increase.[53] So, although statistically significant, evidence so far has show a small increase in risk of both incidence and mortality in CHD with hyperuricemia.

Peripheral arterial disease (PAD) is another manifestation of atherosclerosis, and scarce evidence regarding an association with SU has been published. A cross sectional study among 3987 participants in NHANES 1999–2009, found that higher SU levels were significantly associated with PAD, independently from traditional cardiovascular risk factors.[54] Another study analyzing data from the Multiple Risk Factor Intervention Trial, showed an increased, although non-significant, odds of having PAD in association with hyperuricemia with an OR of 1.23 (95% CI 0.98–1.54). However, a history of gout was associated with an OR of 1.33 (95% CI 1.07–1.66), even after adjustment of underlying hyperuricemia.[55] These findings are regarded as insufficient in order to assume a possible therapeutic approach.[56,57]

Congestive Heart Failure—Increasing SU levels and hyperuricemia have been associated with increased incidence of CHF[58,59] and increased mortality in patients with established CHF.[60–64] Data from the NHANES 2007–2008 estimated increased point prevalences for CHF in hyperuricemic individuals compared with normouricemic individuals with an OR of 2.52 (95% CI 1.58–4.04), and in individuals with gout compared with non-gout with an OR of 2.68 (95% CI 1.88–3.83).[5] An analysis of the Framingham offspring cohort of 4989 adults, with no clinical CHF at baseline, showed that individuals with gout had a 2–3 times higher incidence of CHF and echocardiographic measures of systolic dysfunction. Median follow-up time was 15.9 years. Mortality was increased in participants with gout with an adjusted HR of 1.58 (95% CI 1.40–1.78), compared to people without gout, and this effect was also observed in subgroup analysis comparing individuals with gout and CHF in comparison to those with heart failure but without gout.[65]

However, evidence suggests that increased xanthine-oxidase activity in damaged myocardial tissue results in the production of urate precursors and radical oxygen species, which are responsible for cardiac hypertrophy, myocardial fibrosis, left ventricular remodeling, and contractility impairment.[66] This poses urate as a marker of increased xanthine-oxidase activity rather than actual causative factor. Support for this hypothesis was provided by an analysis on CHF outcomes in patients with and without chronic kidney disease (CKD), which concluded that hyperuricemia is associated with a poor outcome in CHF without CKD but not in patients with CHF and CKD. In the former case, hyperuricemia would be

secondary to increased xanthine oxidase activity, rather than impaired excretion like in CKD.[63] Although there are few therapeutic trials, and data is suggestive of improvements in myocardial function and ejection fraction being secondary to xanthine-oxidase inhibition rather the lowering of SU.[67–71]

Cerebrovascular disease—New evidence has emerged regarding an association between SU and cerebrovascular disease. A study using brain magnetic resonance images (MRI) evaluated the aggregate volume of white matter hyperintense signals in a sample of 177 adults. High normal SU (SU >5.75 mg/dL for men; >4.8 mg/dL for women) concentrations were associated with a significantly increase in white matter hyperintense signals compared to participants with low to moderate SU levels. This association was still significant after adjusting for traditional risk factors.[72] SU has also been postulated as a predictor of poor prognosis and recurrent events in stroke survivors.[73,74]

Results from the NHANES 2007–2008 showed an increased incidence of stroke in individuals with gout with an OR of 2.02 (95% CI 0.98–4.19) and hyperuricemia 1.74 (95% CI 1.16–2.59), in comparison to the control population. Although the risk was increased in women, this difference was not significant.[5] A systematic review and meta-analysis pooled a total of 16 studies including 238,449 adults and after adjusting for known risk factors, hyperuricemia was associated with a 47% (95% CI 1.19–1.76) increased risk of stroke and a 26% (95% CI 1.12–1.39) increased mortality. In this analysis, no significant difference by sex was observed.[75] The intervention trials with ULT have had conflicting results on subclinical parameters,[76–78] and no evidence supporting use of ULT in stroke patients is still available.

In summary, an association between serum urate concentrations and cardiovascular disease is becoming firmly established for hypertension and is an evolving field with still insufficient evidence for atherosclerosis, coronary artery disease, stroke, and congestive heart failure. The first attempts at a leap to causality are being made by the development of interventional clinical trials aimed at lowering serum urate and affecting cardiovascular outcomes.

Renal disease

Urate and renal disease – laboratory and animal models—Almost 90% of the filtered urate is reabsorbed at the proximal tubule by the urate-anion exchanger URAT-1, located at the apical membrane of tubular cells.[17,79] Urate regulation at the tubular level is a complex process that involves several other transporters, and conditions such as Lesch-Nyhan syndrome and tumor lysis syndrome, in which SU levels rise over 10 mg/dl, cause renal damage through urate deposition in the tubuli.[79–81] Deposition of crystals within the tubuli has also been mentioned as an initial phase of the translocation of urate crystals to the interstitium and medulla, a component of the crystal-related nephropathy. This mechanism, which leads to tubular atrophy and vascular degeneration, used to be considered as the explanation for renal damage in gout patients. However, with the decrease in incidence and severity of crystal nephropathy, this diagnosis is now considered only for specific subgroups which include lead intoxication or genetic defeats leading to increased urate production.[79]

However, animal models have shown significant evidence of renal injury and disease in absence of crystal deposition. Systemic and glomerular hypertension with increased vascular resistance and reduced renal blood flow secondary to increased oxidative stress and endothelial dysfunction, was observed in rats with oxonic acid-induced hyperuricemia. In two of these models, changes were reversed by using tempol (a superoxide scavenger) and L-arginine (a substrate for endothelial nitric oxide synthase).[18,82,83] Activation of the renin-angiotensin system (RAS) also contributes to the development of vascular disease of the afferent arteriolar system and glomerular hypertrophy.[22,84] The development of arteriolopathy leads to glomerular hypoxia and ineffective autoregulation mechanisms, which further increases the damage to the glomerulus.[14,19] These changes result from specific mechanisms that involve stimulation of NADPH oxidases with mitochondrial dysfunction,[85] production of reactive oxygen species,[86] activation of the RAS,[13] smooth-muscle cell proliferation,[13] and induction of proinflammatory cytokines.[87] Recent data have also shown a direct effect of urate in tubular cells, promoting a phenotypic transition of renal tubular cells such as epithelial-to-mesenchymal transition by decreasing expression of E-cadherin synthesis.[88] Epithelial-to-mesenchymal transition is considered one of the initial phenomena in renal fibrosis.[89]

Hyperuricemia-induced renal damage has been shown to have a significant effect in animal models with pre-existing renal disease. This has been proven in nephrectomy injury models, were ULT was shown to improve blood pressure, renal function and decrease histologic changes.[21,90] In a model of cyclosporine nephropathy, increasing urate worsened renal disease and ULT ameliorated renal damage.[91,92] An animal model of diabetic mice also showed that reducing SU improved diabetic nephropathy by reducing tubulointerstitial injury with no effect on glomerular damage.[93]

Chronic kidney disease—An association between hyperuricemia, including gout, and CKD has been frequently described in the literature and population studies. Data from NHANES 2007–2008 described a prevalence of CKD stage 3 or more in 19.9% of individuals with gout, associated with an OR of 2.32 (95% CI 1.65–3.26) when compared to individuals without gout. Prevalence in hyperuricemic population was also significantly increased compared to normouricemic population (14.8% vs. 3.3%, respectively), with an OR of 3.96 (95% CI 2.63–5.97). Increased prevalence was observed with increasing values for SU.[5] Although the causality of these observations has been difficult to confirm, due to the increasing SU with declining renal function, evidence from experimental data explained a possible role of SU in the incidence and progression of CKD.

The largest epidemiological study to date, that included 177,570 adults from the U.S. Renal Data System (USRDS) for 25 years, reported an independent association between SU and risk for end-stage renal disease with a HR of 2.14 (1.65–2.77) when comparing the highest with the lowest quartile.[94] Another large cohort study evaluating 21 547 adults of the Vienna Health Screening project, reported a almost double (OR 1.74 [95% CI 1.45–2.09]) increased risk of kidney disease in individuals with SU levels between 7.0–8.9 mg/dL and a triple risk in individuals with levels above 9.0 mg/dL (OR 3.12 (95% CI [2.29–4.25]).[95] A pooled study from the Atherosclerosis Risks in Communities and the Cardiovascular Health Study cohorts and two analyses from the Okinawa General Health Maintenance Association

Study cohort also support an association between SU and the development of end-stage renal disease.[96–98]

In IgA nephropathy, elevated SU has also been reported as an independent predictor for the development of CKD.[99–101] In diabetic patients, elevated SU levels have been described as independent predictor of the development of diabetic nephropathy,[102] micro- and macroalbuminuria,[103] and declining renal function[104] in type 1 diabetes patients. Hyperuricemia has also been associated, after adjusting for possible confounders, with an increased risk of incident CKD (OR 2.10 [95% CI 1.16–3.76]) among type 2 diabetes patients with normal kidney function.[105] However, data analyzing the association between progression of CKD and SU is still not conclusive. A recent study of stage 3–5 CKD middle-aged and elderly Taiwanese adults concluded that elevated urate increased the risk of renal disease only in stage 3 CKD but not in more advanced stages. [106] SU has also been reported as an independent risk factor for progression of kidney disease by other studies,[107,108] while no association has also been reported.[109,110] This information may point to urate as a stronger risk factor for incidence rather progression of CKD.[111]

Treatment with allopurinol in hyperuricemic individuals with normal renal function have shown a beneficial effect on estimated glomerular filtration rate.[39,112] Interventional trials on CKD patients, although scarce and small, have also shown supporting results. A randomized study of allopurinol and placebo in 54 patients with stage 3–4 CKD showed a slowing in disease progression in the treatment arm compared to placebo.[113] Another study that included 113 patients with estimated glomerular filtration rate (eGFR) <60 mL/min/ $1.73m^2$, randomized patients either to allopurinol 100 mg/day or placebo for 24 months. After 24 months, there was no significant change in eGFR the allopurinol group, while a significant decrease in eGFR was noticed in the control group. Allopurinol treatment slowed renal disease progression estimating a HR reduction of 0.53 (95% CI 0.28–0.99). A beneficial effect on cardiovascular endpoints was also observed.[114] A study using a different approach randomized 50 patients with CKD 3–4 already on allopurinol for treatment of mild hypeuricemia, to either continuation or withdrawal of allopurinol. After allopurinol withdrawal, there was a significant acceleration in the decline of renal function as well as worsening hypertension.[115] In a post-hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAAL) trial, where the intervention was treatment with the antihypertensive losartan, a reduction of 6% of renal events was observed for every 0.5 mg/dL reduction of SU. The impact of SU reduction over time on losartan's renoprotective effect was estimated by adjusting for the residual SU in the analysis of renal events, and after observing a mild reduction on losartan's effect (from 22% to 17%), the investigators concluded that 1/5 of the observed losartan's renoprotective effect was attributed to its uricosuric effect.[116] In diabetic patients with diabetic nephropathy, a small randomized placebo-controlled trial of 40 patients showed a reduction of proteinuria in patients treated with allopurinol.[117]

Acute kidney injury—Hyperuricemia and acute kidney injury, via crystal-dependent mechanisms, have usually been associated in the context of tumor lysis syndrome. However, based on the observations of experimental models on crystal-independent renal injury, a possible association of SU and acute kidney injury (AKI) has been described. In a small trial

evaluating the incidence of postoperative AKI in patients undergoing high-risk cardiovascular surgery, SU greater than 6 mg/dL was associated with a four-fold increase for AKI (OR 3.98 [95% CI 1.10–14.33]).[118] Poor survival after coronary artery bypass grafting has also been associated with increasing SU levels.[119] A more recent study of 190 patients who underwent cardiovascular surgery reported increasing incidences of AKI (defined as absolute increase in SCr ≥0.3 mg/dL from baseline within 48 hours after surgery) with increasing levels of SU. In the multivariate analysis, SU levels starting from equal or above 5.5 mg/dL were associated with an increased risk, ascending up to a 35-fold (OR 35.4 95% [CI 9.7–128.7]) with SU equal or above 7 mg/dL.[120] A double-blind, placebo-controlled, randomized interventional trial using pre-operative rasburicase in hyperuricemic patients undergoing high-risk cardiovascular surgery showed no benefit on postoperative serum creatinine. However, a decrease in of the urine neutrophil-associated lipocalcin (a predictive marker of AKI in cardiovascular surgery patients) was reported in the rasburicase-treated subjects.[121] Information on this subject is still scarce and inconclusive.

Urolithiasis—Urate nephrolithiasis represents 7 to 10% of all nephrolithiases in the United States. [122] The vast majority of individuals suffering from urate kidney stones are neither hyperuricemic or suffer from gout, since the usual abnormality observed in these individuals is consistently acidic urine (pH <5.5). [123,124] However, a large population study did report an association between the diagnosis of gout and an increased risk of incident kidney stones (RR 2.12 95% CI [1.22–3.68]).[125] Hyperuricosuria, decreased urinary pH and low urinary volume are considered the three main factors involved in the development of urate nephrolithiasis.[80] The role of hyperuricemia and gout as risk factors may still not be clear, especially since studies have shown that most gout patients are urate underexcretors.[124,126] A stronger association between urate nephrolithiasis with type 2 diabetes mellitus and obesity has been described and explained in the basis of predisposition to an acidic urinary environment.[80,122]

Evidence on urate crystal-independent mechanisms of renal injury, coupled to epidemiological data, show a role for urate in the development of CKD. However, its importance in the progression of the disease and the potential use of ULT in CKD patients is still unclear. Further clinical trials in CKD patients are needed, as well as further information on the possible role of SU as a risk factor for AKI.

Metabolic disease

Urate pathways and fructose – laboratory and animal models—The increased renal reabsorption of SU at the proximal tubules secondary to hyperinsulinemia, has been regarded as the main hypothesis for the association between hyperuricemia and the metabolic syndrome (MS).[127,128] However, models incorporating fructose metabolism are uncovering the contributory role of urate in the metabolic syndrome. Fructose consumption, either in the forms of table sugar or high-fructose corn syrup (in beverage and food sweetening), has increased in the last 30 years and epidemiological data has shown similar increments in obesity and associations with certain components of the MS.[129–133] Fructose is phosphorylated by the enzyme fructokinase, which by having no negative-feedback

mechanism works uninterruptedly, causing intracellular phosphate and ATP depletion and increased activity by the adenosine monophosphate deaminase, leading to increased levels of urate.[134,135] An overlap of the increasing consumption of fructose and a corresponding trend of SU has been recognized.[136] Fructose-induced hyperuricemia has been proven to result in the development of insulin resistance (IR), hypertension and renal injury in several animal models.[137–140] This process has also been reversed by the administration of xanthine oxidase inhibitors (allopurinol and febuxostat) and uricosuric drugs (benzodiarone), suggesting a dependency on SU concentrations and not xanthine oxidase activity.[139,140] Recent data on a trial using oxonic acid on rats fed with physiologic concentrations of fructose, showed that although hyperuricemia did not increase body weight, blood pressure or triglyceride levels, it did cause structural renal damage and significant increase in plasma insulin levels.[141] The latter, through development of IR, is regarded as the potential central promoter of the MS.[142–144]

Based on findings and observations from experimental data, two different mechanisms that could explain the induction of IR, and hence hyperinsulinemia, have been proposed [see Figure 3].[111] First, hyperuricemia reduces endothelial NO bioavailabilty.[10,11] Since NO is necessary for glucose uptake in skeletal muscle, alterations in carbohydrate metabolism occurs secondary to this deficiency.[145] Hypertension, another result of reduced NO bioavailability and damage to the endothelium, has also been pointed as a possible mediator of the MS.[146] A second important mechanism results from the inflammatory and oxidative changes in adipose tissue secondary to exposure to elevated concentrations of urate. Intracellular urate in adipocytes, probably after translocation by URAT-1 transporters, increase oxidative stress by an increase in the enzymatic activity of the reduced form of the nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, giving rise to reactive oxygen species which lead to protein nitrosylation, lipid peroxidation and further NO reduction.[86] This also induces macrophage infiltration, liberation of other inflammatory molecules such as MCP-1 and reduction of adiponectin.[146,147] These inflammatory and oxidative changes in adipocytes have been shown to cause MS in obese mice.[148] A study with obese hyperuricemic mouse hyperuricemic showed that after lowering urate levels with allopurinol the proinflammatory endocrine imbalance was improved, with reduction of macrophage infiltration in adipose tissue, increase in adiponectin levels and reduction in IR.[147]

Insulin resistance and diabetes—As already seen in animal models, human studies have also shown an inverse correlation between high urate levels and insulin sensitivity.[149,150] A large population study on 53,477 Korean adults showed that SU levels were independently correlated with IR and that this risk, as that for the metabolic syndrome, was maintained when patients were within the normal range.[151] Although a causal association is still in debate, a recent 15-year follow-up study on 5,012 US non-diabetic adults has supported the contribution of SU to IR. After using regression models, it demonstrated that individuals with hyperuricemia (defined as >7.0 mg/dL) were more likely to develop IR and pre-diabetes, HR 1.36 (95% CI 1.23–1.51) and 1.25 (95% CI 1.04–1.52), respectively.[152] Another study also supported a higher risk of developing hyperinsulinemia with increase baseline urate levels in non-diabetic patients.[153] Although interventional

studies are still missing, a clinical trial of ULT with benzbromarone in patients with CHF, lowering SU showed an improvement in IR.[71]

Type 2 diabetes mellitus, the final expression of IR, has also been associated with increasing serum urate concentrations in epidemiological studies. A 15-year follow-up study reported an increased risk for the development of diabetes in individuals with hyperuricemia (HR 1.87 [95% CI 1.33–2.62]), hyperuricemia.[152] An increased risk has also been reported by different cohorts.[29,154–158] Data from NHANES 2007–2008 showed that individuals with hyperuricemia presented an increased risk for diabetes (OR 1.63 [95% CI 1.13–2.34]), and that this risk had a dose-dependent association with SU levels. Diabetes prevalence among individuals with gout was also increased in comparison to individuals without gout, 25.7% and 7.8% respectively, reflecting an increased risk for diabetes among individuals with gout.[5] However, data on this relation is still not conclusive with several studies indicating either no association between SU and diabetes,[159] or even an inverse relationship between both.[160–162] Although based on epidemiological data causality is still controversial, use of SU as a predictor of all-cause mortality in type 2 diabetic patients was recommended in a study carried out on a cohort of 535 diabetic adults. This association remained significant after adjusting for other co-variables.[163]

Metabolic syndrome—The MS represents a cluster of physiological and anthropometric abnormalities (IR, elevated blood pressure, truncal obesity, hypertriglyceridemia and low high-density lipoprotein-cholesterol (HDL) and is regarded as a risk factor for the development of diabetes and cardiovascular diseases. An association between MS and hyperuricemia has been already been well-described. An analysis of NHANES III data showed an increasing prevalence of the MS with increasing levels of SU, equal or above 10 mg/dL in comparison to the individuals with levels less than 6.0 mg/dL (70.7% and 18.9% respectively). A significant difference in prevalence between individuals with and without gout was also shown (62.8% and 25.4% respectively).[164] The increasing risk of MS in individuals with higher SU levels has also been described by other studies,[165,166] and even the elevated SU levels have also been observed to be significantly increased by the number of components of MS.[165,167,168] An increased risk has even been described in individuals with high-normal SU levels in a Korean cohort.[169]

Besides IR and hypertension, associations between SU and other individual components of the MS have also been described. In a study on 11,182 subjects over 65 years old, triglyceride levels and waist circumference have shown a positive correlation with urate levels, while HDLc showed a negative correlation.[170] These observations had been previously reported on patients with high cardiovascular risk and a population based study in Spain.[171,172] A strong relationship between hyperuricemia, gout and obesity has been well documented, and data from a NHANES 1988–1994 and 2007–2010 analysis of has shown a progressively greater prevalence of gout in higher BMI categories.[173] However, direct causality is still not clear and it may involve leptin, adiponectin and inflammation on adipocytes [see Figure 3].[174] Interestingly, a study analyzing data from individuals with and without hyperuricemia in Taiwan, identified obesity and hypertriglyceridemia as possible potentiating factors on SU for the development of gout.[175]

Neurological disorders

Antioxidants effects of urate—In comparison to other mammals, higher levels of urate are secondary to the evolutionary loss of urate oxidase.[176,177] This mutation was seen by as beneficial and part of adaptation by several authors, that postulated the presence of urate as an stimulant with positive effects in cognition, alertness and motivation,[178] or an anti-aging effect through its ability to prevent oxidative damage.[179] Although the theories of urate's antioxidant capacity were ignored due to the association of high urate levels and cardiovascular risk, evidence on its neuroprotective effects and association with neurodegenerative disorders have resurfaced this aspect.

Urate can act as a powerful scavenger for peroxynitrite,[180] peroxyl and hydroxyl radicals,[181] and has been shown to reduce oxidative damage in DNA molecules.[182] In studies using cellular models of neurodegeneration, reduced oxidative stress and cell death have been associated with urate, and even one study using a mouse model of Parkinson's disease showed suppressed oxidative stress and death of dopaminergic cells.[183,184] In 1994, the first study reporting an association of SU and Parkinson disease in post-mortem human tissue samples showed that urate was significantly reduced in the substantia nigra of Parkinson patients, and its addition decreased oxidation of dopamine in the caudate nucleus and substantia nigra.[185]

Parkison's disease and other neurodegenerative conditions—The largest prospective study evaluating the relationship between hyperuricemia and the risk of developing Parkinson's disease analyzed data from 18,018 men from the Health Professional Follow-up Study. During the observation period, 84 subjects were diagnosed with Parkinson's disease and after adjusting for other variables, the rate ratio for the highest quartile of uricemia compared with the lowest was 0.43 (95% CI 0.18–1.02).[186] Data from a more recent study, the Atherosclerosis Risk in Communities (ARIC) study, reported a similar OR, 0.4 (95% CI 0.2–10), when comparing extreme quartiles of plasma urate.[187] Data regarding risk of Parkinson's disease on individuals with gout has also been reported by two studies. An analysis of the General Practice Research Database, which includes over 3 million adults in the UK, reported that individuals with a previous history of gout had a lower risk, OR 0.69 (95% CI 0.48–0.99) of developing Parkinson's disease. This association was only seen in men.[188] Another study based on an 8-year median follow up of a Canadian cohort, reported an adjusted relative risk of 0.70 (95% CI 0.59–0.83) among those with gout.[189] A recent review on this subject suggests, although still not at a clinical level, the feasibility of using SU as risk, diagnostic and prognostic marker for Parkinson's disease.[176]

Data supporting this association has also been observed in other neurodegenerative diseases. In multiple sclerosis, a study showed that lower urate levels correlated with a worst prognosis, this expressed as relapses.[190] Meanwhile a study on Huntington's disease that higher SU levels correlated with a slower disease progression, and evidenced a trend of decreased worsening of motor function with increasing urate.[191] Although evidence on interventional trials is lacking, a small trial with 11 multiple sclerosis patients treated with inosine (aimed at increasing SU levels) showed clinical improvement in 3 of the patients,

and no disease progression on the rest.[192] Evidence on this association is still lacking and further studies are needed in order to determine the actual nature of these observations.

COMORBIDITIES ASSOCIATED TO CALCIUM PYROPHOSPHATE DIHYDRATE CRYSTAL DEPOSITION DISEASE

Pseudogout, as initially described by McCarty and colleagues, is just part of the spectrum of CPPD crystal deposition disease that also includes pyrophosphate arthropathy, asymptomatic chondrocalcinosis and unusual presentations such as pseudo-rheumatoid arthritis or crowned dens syndrome.[3,193,194] Population studies using radiological evidence of chondrocalcinosis have estimated prevalence ranging between 7% and 10%, usually in population over 60 years, and have proven a positive association with age.[195–198] However, prevalence can vary depending on the method of identification. Studies examining synovial fluid of osteoarthritic joints at the time of joint replacement have reported a 25–43% prevalence of CPPD crystals.[3] Data on CPPD, as well as on the associations with other comorbidities is still scarce. Most relevant evidence on these associations is presented in the following sections.

Osteoarthritis

An association between CPPD deposition disease and osteoarthritis (OA) has been discussed and suggested for years; however the precise nature of this relationship is still unclear, and the existence of common risk factors (e.g. aging and joint injury), makes studying the relationship quite complex and challenging.[199,200] CPPD and other calcium crystals, such as basic calcium phosphate crystals, have been shown to generate calcium oscillations in articular chondrocytes[201] and a prolonged inflammatory response which can contribute or amplify articular degeneration and joint damage.[202,203] Increased transcription of progressive ankylosis homolog gene (ANKH), whose mutations have been described in familial forms of CPPD disease,[204] has been reported in OA meniscal cells.[205]

The European League Against Rheumatism (EULAR) recommendations on CPPD deposition disease, analyzed the association with OA taking into account four cross-sectional and five case-control studies. It estimated that people with OA were almost three times more likely to have CPPD, OR 2.66 (95% CI 2.00–3.54).[199] A study included two cohorts of people with knee OA and radiographic Kellgren scores of greater than or equal to 2 used MRI to explore the relation between radiographic chondrocalcinosis and OA progression. After 30 months of imaging and follow up, cartilage loss, used as a proxy for progressive OA, showed no correlation with the presence of chondrocalcinosis.[206] Evidence on this subject is still not conclusive, and although calcium crystals may be involved in the process of OA, more studies are needed.

Metabolic and endocrine disorders

A relationship between hemochromatosis and CPPD disease has been described. A study of 178 patients diagnosed with hereditary hemochromatosis and not yet treated with phlebotomy, showed a 30% prevalence of chondrocalcinosis and a positive correlation between the number of joints involved with age, ferritin level and PTH 44–68.[207] An older

case series of 54 patients with hemochromatosis, reported a significant association, OR 6.81 (95% CI 2.02–22.95), with chondrocalcinosis.[208] Although still in debate, the actual significance of this association may be relatively small. This was shown by a study that carried out systematic genetic testing in 128 patients with chondrocalcinosis and pseudogout, showing a low prevalence of C282Y homozygotes and C282Y/H63D compound heterozygotes (1.6% and 3.1%, respectively).[209]

The 2011 EULAR report on CPPD disease pooled data from five studies described an association between CPPD deposition disease and hyperparathyroidism, showing that patients with hyperparathyroidism were three times more likely to have CPPD than controls (OR 3.03 95% CI [1.15–8.02]).[199] Triggering of pseudogout attacks by parathyroidectomy has also been reported been reported by some studies.[210,211] However data on this association is still scarce.

A cross sectional study of 72 patients with intestinal failure and in parenteral nutrition, showed a significant association between hypomagnesemia and chondrocalcinosis. Compared to healthy controls, these patients with chronic hypomagnesemia presented a higher prevalence of chondrocalcinosis (16.6% vs 2.7% in controls), and prevalence of chondrocalcinosis was significantly higher, OR 13.5 (95% CI [2.76–127.3]), in patient with lower serum magnesium levels.[212] Reports on Gitelman's syndrome and chondrocalcinosis support this association.[213,214] CPPD arthropathy or pseudogout can be the onset of presentation of Gitelman's syndrome, and this disease should be considered in the differential of younger patients presenting with CPPD deposition disease.[215]

Hypophosphatasia, gout, ochronosis, familial hypocalciuric hypercalcaemia, X-linked hypophostatemic rickets, Wilson's disease, and acromegaly are additional diseases that have been linked to CPPD disease. However, data on these associations are only based on case reports.[216]

CONCLUSIONS

The clinical significance of asymptomatic hyperuricemia and gout as risk factors for various comorbidities is being recently supported by the emergence of new data from experimental, epidemiological and clinical intervention trials (See Table 1). Evidence available is supportive of a causal role of hyperuricemia on hypertension, leaving SU as a possible therapeutic target, especially on early stages. Although interventional data from small trials is available and does suggest a benefit, larger trials are needed to collect enough evidence to support indication of ULT. Evidence on CHD and stroke although suggesting, is still not clear and required further studies. The association between CHF and urate is probably indirect and related to an increased activity by xanthine oxidase, and benefit of xanthine-oxidase inhibition is still not conclusive. Cardiovascular comorbidities are nowadays important to be considered in the management of gout patients.

Although SU was initially not considered to be a causal factor for the development of the metabolic syndrome, fructose-fed animal models have shown evidence to involve urate in the pathological process of IR. This association requires further studies but poses an interest

relation between the overlapping growths of their respective prevalences. An association between hyperuricemia, gout and diabetes however, is still not clear. The relationship between hyperuricemia and CKD incidence is also becoming clearer in the light of new experimental and epidemiological evidence, however the relation of effects on CKD progression are still not conclusive. Recent data on AKI deserves further attention. The associations between SU and neurodegenerative diseases are still not clear, and further evidence is needed to show if this just represents an observation or a potential therapeutic strategy.

Calcium deposition diseases, such as CPPD, still represent a low proportion of crystal arthropathies and studies on the subject are still scarce. Although interest on the role of calcium crystals in the development of OA is arising, data is still lacking in order for conclusion to be drawn. The association between CPPD deposition disease and several metabolic and endocrine disorders has been established based on several small studies; however the association is still small to consider an active search of these in patients with CPPD disease.

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Key points

- Recent evidence has shown that asymptomatic hyperuricemia, as well as hyperuricemia in gout patients, plays a significant role in the development of cardiovascular comorbidities.
- In addition to an already proven association between hypertension and hyperuricemia, interventional trials are now 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.
- A link between hyperuricemia, insulin resistance and the metabolic syndrome has been shown by fructose-fed animal models, and may explain the association between two 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.

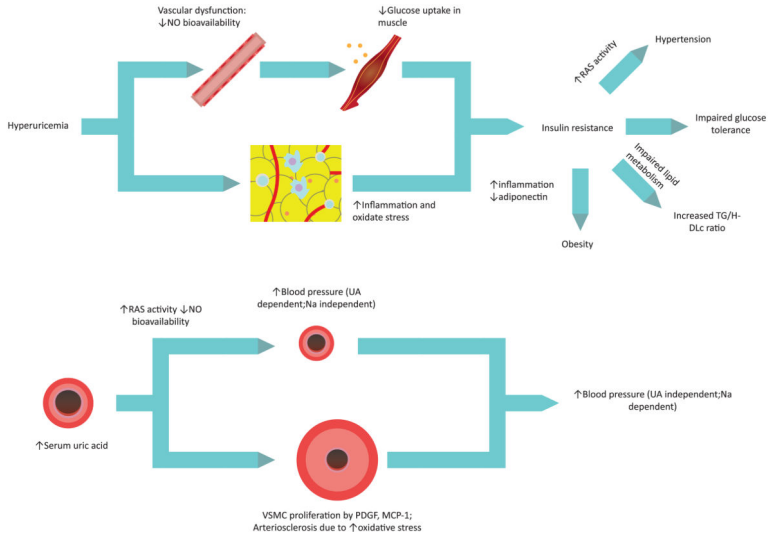

Figure 1.

Proposed two-stage Urate-mediated hypertension

An initial stage of urate-dependent vasoreactive hypertension is induced. Later, when anatomical changes that include wall thickening and smooth muscle proliferation have occurred, a second and definitive sodium-dependent hypertension is established. Adapted with permission from *Feig, DI, The role of urate in the pathogenesis of hypertension in the young. J Clin Hypertens (Greenwich), 2012. 14(6): p. 346–52.*

RAS = renin-angiotensin system; NO = nitric oxide; UA = urate; VSMC = vascular smooth muscle cell; PDGF = platelet-derived growth factor; MCP-1 = monocyte chemotactic protein-1; Na = sodium

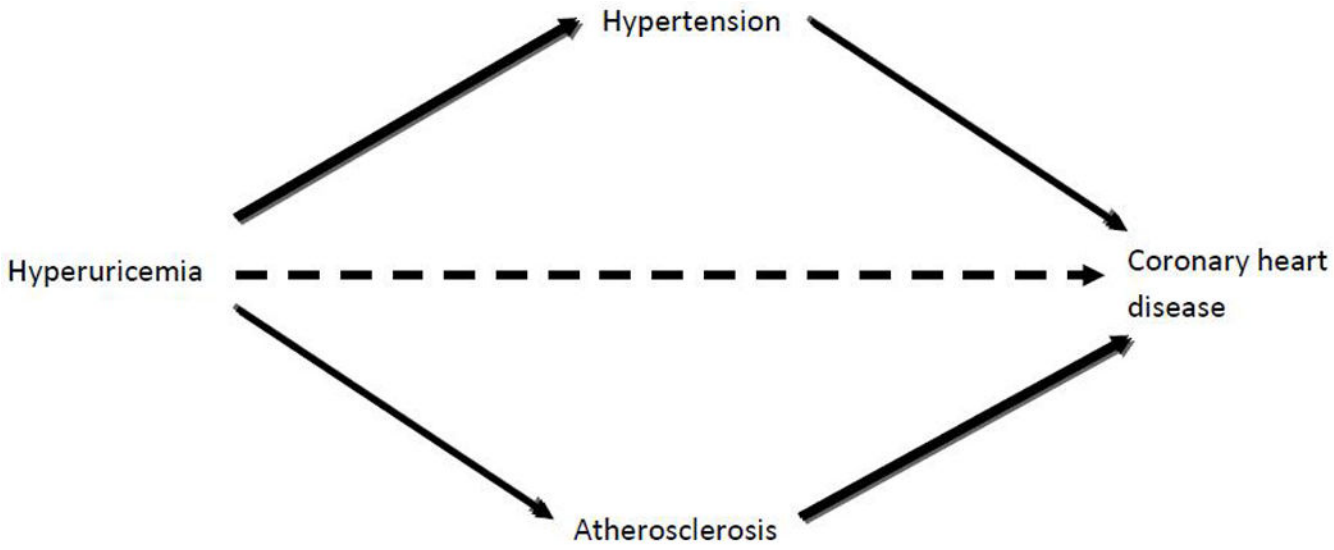

Figure 2.

Association and causality between hyperuricemia and coronary heart disease

Hyperuricemia has an indirect effect in the development of coronary heart disease through the development of hypertension and atherosclerosis. However, evidence on a direct and independent effect (dashed arrow) on the development of coronary heart disease is still not conclusive. Adapted from *Gaffo, A.L., N.L. Edwards, and K.G. Saag, Gout. Hyperuricemia and cardiovascular disease: how strong is the evidence for a causal link? Arthritis Res Ther, 2009. 11(4): p. 240.*

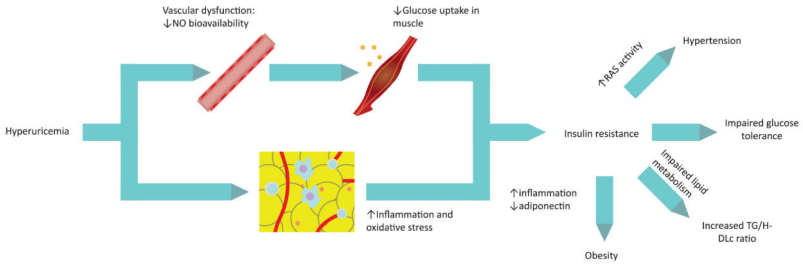

Figure 3.

Hyperuricemia, insulin resistance and the metabolic syndrome

Experimental models have shown that hyperuricemia-induced vascular dysfunction, inflammation and increased oxidative stress lead to insulin resistance, which later leads to impaired glucose tolerance and predisposes to the other components of the metabolic syndrome.

NO = nitric oxide; TG = triglycerides; HDLc = high-density lipoprotein-cholesterol; RAS = renin-angiotensin system.

Table 1

Comorbidities and their association with hyperuricemia and gout

Comorbidity	Evidence on association and causality	Evidence on impact of urate therapies
Hypertension	Several population studies have proven an independent association between SU and development of hypertension.[32,33] SU plays a key role in the initial stages of the development of hypertension.[217]	Small-sampled controlled studies have shown BP reduction with ULT in young individuals[37,38] and adults.[39] However, evidence to recommend use of ULT is still not conclusive. [40]
Coronary heart disease	Although still not conclusive, evidence shows a small but significant increased risk of CHD in individuals with hyperuricemia,[52,53] and patients with gout. [51]	Trials on the use of allopurinol and angina exist, although evidence on CHD incidence and prognosis is still lacking.
Congestive heart failure	Although a constant association with increased incidence[58,59,65] and mortality,[60,61] causality is still in debate since hyperuricemia may just reflect increased xanthine oxidase activity.[6663]	Small trials showing improvement in myocardial function and ejection fraction with allopurinol suggest benefits secondary to xanthine-oxidase inhibition rather than SU lowering.[69,70,71]
Stroke	Associations with cerebral ischemia, [72] increased incidence of stroke[75] and poorer prognosis in stroke patients have been reported.[73,74] However causality is still not clear.	Trials using ULT have shown conflicting results in subclinical parameters.[76–78]
Chronic kidney disease	Experimental evidence on crystal-independent renal injury models[82–84] have supported epidemiological evidence for a causative role of hyperuricemia on CKD.[95–97] However, data on effects of disease progression are still not conclusive.[106,110]	Interventional studies with allopurinol have shown improvement in eGFR in normal individuals[39,112] and a decrease in renal function deterioration in CKD patients.[113–115] Data is still scarce to generalize recommendations for use of ULT.
Insulin resistance and metabolic syndrome	Experimental data has shown a causative role for UA in the development on IR and an association with the development of IR[151,152] and the MS has been established.[165,166,169] Associations with dyslipidemia[170] and obesity have been reported. [173]	A role for ULT in animal models with MS has been shown,[140,147] and improvement in IR was seen in one trial with CHF patients.[71] Further trials are needed.
Type 2 diabetes mellitus	Increasing incidence in individuals with hyperuricemia has been shown.[152,154,155] Studies studying an association between gout and diabetes are still not conclusive, with some studies even showing an inverse relation between both.[159,160,162]	Data on this subject is still lacking to consider further recommendations.
Neuro-degenerative disorders	An association between hyperuricemia and a decreased incidence with Parkinson's Disease[186–188] as a slower development of multiples sclerosis[190] and Huntington's disease has been reported. Data on the subject is still scarce.[191]	A small trial in multiple sclerosis patients showed clinical improvements in 3 of the patients while increasing SU with inosine.[192] Further trials are needed.

SU = urate; UA = urate; ULT = urate-lowering therapy; CHD = coronary heart disease; eGFR = estimated glomerular filtration rate; CKD = chronic kidney disease; IR = insulin resistance; MS = metabolic syndrome; CHF = congestive heart failure.