Cardiovascular and renal effects of hyperuricaemia and gout

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SUMMARY

A number of epidemiological studies have reported an association between serum uric acid levels and a wide variety of high-risk conditions including hypertension, insulin resistance, and kidney and cerebro-cardiovascular disease. All things considered, serum uric acid may induce cardiovascular and kidney events both directly and indirectly by promoting other well-known mechanisms of damage. While asymptomatic hyperuricemia is currently not considered to be an indication for urate lowering therapy, there is growing evidence indicating a linear relationship between pharmacological reduction in serum uric acid and incidence of cardiovascular and renal events.

Key words: hyperuricaemia, gout, CV risk, kidney, organ damage.

Gout is the commonest cause of inflammatory arthritis in men, and its prevalence has gradually increased among the general population over the last few decades. Hyperuricemia is the most important risk factor for the development of gout, and since serum uric acid (SUA) levels tend to be higher in men, clinical gout is about five times more common in men than in women. Despite this strong association, the majority of patients with hyperuricemia do not develop gout; the annual incidence of gout is estimated at only 5% in patients whose serum urate levels are above 9 mg/dL (1). While asymptomatic hyperuricemia is currently not considered to be an indication for urate lowering therapy, there is strong evidence that increased SUA levels and gout are associated with subclinical atherosclerosis and an increased risk of cardiovascular (CV) (2) and renal events (3). Experimental studies suggest there are several pathogenetic mechanisms linking SUA to the development of atherosclerotic damage. Johnson and co-workers developed an animal model of mild hyperuricemia in which rats were made unable to metabolize uric acid to allantoin by means of the ingestion of oxonic acid (OA), a uricase inhibitor that reproduces the enzyme deficiency which the human species developed during evolution (4). Hyperuricemic OA-treated rats have been shown to develop hypertension by a renal mechanism linked to the inhibition of nitric oxide (NO), activation of the renin angiotensin system (RAS), and development of arteriolosclerosis (5). Prolonged hyperuricemia in rats also causes progressive renal injury via a crystalline-independent mechanism (5) and can accelerate the progression of renal disease (6) through vasoconstriction and increases in glomerular pressure (7). Finally, uric acid stimulates synthesis of the monocyte chemoattractant protein-1 (MCP-1) by rat vascular smooth muscle cells (VSMCs) (8), which is known to play a key role in promoting macrophage infiltration in atherosclerotic vessels (9). Whether uric acid per se might be considered atherogenic or merely an independent marker of increased disease risk will be discussed in the present review.

■ SUA AND CV RISK FACTORS

A number of epidemiological studies have reported an association between SUA levels and a wide variety of high-risk condi-

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tions including hypertension, insulin resistance, and kidney and cerebro-cardiovascular disease. Moreover, the sharp rise in the prevalence of hypertension, obesity, diabetes and chronic kidney disease (CKD), has also been associated with a progressive rise in SUA levels in the general population (10). Mean uric acid levels in men increased gradually from less than 3.5 mg/dL in the 1920s to 6.5 mg/dL in the 1970s. Interestingly, the connection between uric acid and CV risk is observed not only with frank hyperuricemia, but also when uric acid levels are in the so-called normal to high range (4.5-5.5 mg/dL) (11).

It has been pointed out that the increase in uric acid levels in patients with atherosclerotic vascular disease might simply be a result of a reduction in its renal excretion due to concomitant factors, such as reduced glomerular filtration rate (GFR), hyperinsulinemia, and renal vasoconstriction, and the use of diuretics. It may also reflect an increase in the generation of uric acid caused by alcohol or excessive fructose intake, tissue ischemia, or oxidative stress (3).

Hypertension

A positive association between SUA and hypertension was first observed over a century ago (12). In a multicenter study on 2,145 hypertensive Taiwanese patients, the presence of hyperuricemia was 1.5 and 1.7 fold higher in hypertensive men and women, respectively, when compared to the general population (12). Although the relationship between uric acid and blood pressure is confounded by numerous factors, including age, diabetes, obesity, alcohol use, sodium intake or volume status, a link between hyperuricemia and hypertension has been confirmed over the years by several large studies.

Finally, a recent meta-analysis of published prospective studies indicates that hyperuricemia is associated with a 41% increase in the future risk of incident hypertension, regardless of traditional risk factors. As is the case for the relationship between SUA and other CV outcomes, the relationship between SUA and blood pressure appears more pronounced in younger individuals and women (13). Experimental studies conducted both on animals and humans suggest the existence of a two-step pathogenetic mechanism linking SUA to the development of hypertension (14-16). Uric acid initially activates the RAS and suppresses NO, leading to a uric acid-dependent increase in systemic vascular resistance. This is followed by a uric acid-mediated vasculopathy involving renal afferent arterioles, which then results in late sodium-sensitive hypertension.

Furthermore, a double-blind, placebo-controlled, crossover trial of 30 hyperuricemic adolescents with hypertension demonstrated that lowering uric acid with allopurinol led to a lowering of blood pressure over a 4-week period (17). Although these data support a pathogenetic role of uric acid in the development of hypertension in this specific demographic context, whether these findings are applicable to an adult population remains to be confirmed.

Metabolic syndrome and diabetes

The prevalence of metabolic syndrome (MS) (18-20) and each one of its components (21) increases in a graded fashion as SUA levels increase, and this has led some to propose that hyperuricemia be included in the definition of MS. Furthermore, it has been hypothesized that the occurrence of high SUA levels in MS may not merely be a consequence of hyperinsulinemia (22). In fact, SUA may play an important role in the pathogenesis of MS due to its ability to inhibit NO bioavailability and thereby induce endothelial dysfunction. SUA has been shown to predict the development of MS in humans (23), and is positively associated with serum glucose in healthy subjects (24). However, a similar association has not been confirmed in diabetic individuals (25), as low SUA levels have been reported in hyperglycemic states (26). A recent meta-analysis describing the relationship between SUA levels and risk of type 2 diabetes, showed that each 1 mg/dL increase in SUA results in a 17% increase in new onset diabetes in the general population (27). More recently, an independent

predictive role for SUA in the development of diabetes has been reported in various clinical settings, from normal subjects (28) to high (29) and relatively low-risk hypertensive patients (30).

Interestingly, increasing the amount of fructose in the diet of rats resulted in escalating levels of hyperuricemia (31). They developed hypertension, hypertriglyceridemia, hyperinsulinemia as well as glomerular hypertension, renal cortical arteriole vasoconstriction, and preglomerular arteriolopathy (31). Unlike the metabolic effects of other sugars, fructose induces hyperuricemia by stimulating nucleotide catabolism via the conversion of hepatic ATP to ADP by fructokinase; as ATP is consumed, AMP accumulates and stimulates AMP deaminase, resulting in uric acid production (32). An epidemiological analysis revealed that sugar-sweetened beverages, a major source of fructose, raise SUA levels and are associated with an increased risk of gout, hypertension, and diabetes (33).

Cardiovascular and renal damage

While some studies failed to find a correlation between SUA and organ damage, (34, 35) most data available in the literature report a strong, independent association between SUA levels and clinical signs of atherosclerosis, including carotid arterial intima-media thickness (36-39), brachial-ankle pulse wave velocity (40), atherosclerotic renal artery disease (41), and peripheral artery disease (42).

A relationship between SUA levels and the severity of coronary artery disease (CAD) was described for the first time by Tuttle et al. (42) in a group of patients undergoing cardiac angiography. Later, an association between hyperuricemia and coronary artery calcification (CAC) was confirmed in studies on patients with underlying risk factors for CAD such as type 1 diabetes, long-standing hypertension, or MS (44-47). More recently, Krishnan et al. (48) found a direct correlation between the prevalence and severity of CAC and SUA concentrations in healthy young adults, confirming the hypothesis that uric acid may be involved in the pathological process of atherosclerosis, regardless of conventional risk factors.

SUA has also been linked to left ventricular hypertrophy (LVH) in hypertension (38), and in apparently healthy Japanese men (49, 50). Iwashima et al. also demonstrated that uric acid is independently associated with left ventricular mass index (LVMI) and suggested that the combination of hyperuricemia and LVH is an independent and powerful predictor of CV disease (51). The association between SUA and LVMI may be due to the clustering of SUA with other risk factors, or to clinical conditions such as renal dysfunction, severity of hypertension, and obesity. Moreover, SUA may reflect the production of superoxide and resulting oxidative stress via the xanthine-oxidase (XO) system (52). On the other hand, cardiac hypertrophy might be, at least in part, attributable to an increase in SUA itself, via stimulation of endothelial dysfunction, VSMC proliferation, and inflammation (53, 54).

SUA levels are a function of the balance between the breakdown of purines and the rate of uric acid excretion; therefore, renal impairment may be involved in hyperuricemia. Decreased urate filtration occurs in renal insufficiency, and decreased tubular secretion of urate is a common finding in patients with acidosis. Lastly, enhanced reabsorption of uric acid in the nephron is thought to contribute to hyperuricemia under diuretic therapy (55). The association of gouty arthritis, elevated SUA levels and renal disease is historically well documented (56). Chronic urate nephropathy may be the result of substantial renal deposition of urate crystals, leading to interstitial fibrosis and arteriolosclerosis (57). However, urate deposition is an uncommon finding in patients with gout who undergo renal biopsy (58), while arterial and arteriolar nephrosclerosis are more commonly observed. Mild hyperuricemia has been associated with sub-clinical signs of renal damage, such as ultrasound detected reduction in renal volume and increased renovascular resistive index by Doppler evaluation (59). Furthermore, a positive association between SUA concentration and degree

of urinary albumin excretion has been described in patients with type 2 diabetes, (60, 61), with hypertension (34, 38, 62) and in a large cohort of pre-hypertensive subjects with normal renal function (63). Finally, increased SUA levels have been linearly associated with the severity of tubular atrophy observed in the biopsies of patients with IgA nephropathy (64). Consistent with these findings, an animal model proved that mild hyperuricemia accelerates renal damage progression through increased systemic blood pressure and endothelial dysfunction due to cyclooxygenase (COX)-2 and thromboxane cascade abnormalities which in turn contribute to the development of glomerular arteriosclerosis (65, 66).

Hyperuricemia has been independently associated with an increased risk of CKD in cross-sectional studies in Europe, Asia, USA, and China both in the general population and in hypertensive patients (55, 67-70). Despite this evidence, an elevated SUA level is currently not universally regarded to be a risk factor for CKD (71), because of the frequent coexistence of other, more traditional risk factors for CKD, such as diabetes, hypertension, dyslipidemia, obesity, smoking and insulin resistance.

SUA as a predictor of CV and renal diseases

Patients with hyperuricemia show an increased rate of CV death or morbidity (72-76) mainly in high risk populations (77-79). In the LIFE study (80), CV events were related to SUA levels, although only in women, after adjustment for Framingham risk score was made. Similar results showing a stronger predictive role of SUA in women were found in more than 4,300 individuals enrolled in the Rotterdam study (81) and in an analysis of the NHANES I (82). Interestingly, an independent link between myocardial infarction and both gout and hyperuricemia was reported in the MR-FIT study (83) with a 6.5 year follow up conducted on 12,866 men with no previous history of coronary heart disease (CHD). Two recent meta-analyses of prospective studies showed a significant independent

association between even mild hyperuricemia and CHD incidence (HR 1.09) and death (HR 1.16) (84), as well as stroke rate (HR 1.47) and mortality (HR 1.26) (85).

It has been pointed out, however, that many studies did not account for the confounding effect of decreased kidney function, a well-known risk factor for CV disease (72, 74, 82). This may have led to an overestimation of the association of hyperuricemia and CV incidents. Nevertheless, in several recent studies, uric acid levels were still associated with CV morbidity, even after adjusting for decreased kidney function (86, 87). In the study by Neri et al., (86), the association between SUA level and CV disease was stronger in patients with advanced CKD, a finding debated (88) though confirmed by a subset analysis of 839 patients enrolled in the MDRD trial (89), as well as in other studies conducted on patients under renal replacement treatment (90-92).

Finally, while it has been suggested that hyperuricemia plays an active role in causing graft injury (93), increased SUA levels showed no additive value to the Framingham risk score for predicting myocardial infarction, coronary artery revascularization, or cardiac death in kidney transplant recipients (94).

SUA may be directly toxic to the kidney. Moreover, it may mediate aspects of the relationship between hypertension and kidney disease via effects on renal vasoconstriction and systemic hypertension; therefore, it is assumed to be a risk factor for CKD progression. Cohort studies have shown contrasting results on whether uric acid is an independent risk factor for the development of kidney disease (95, 96). Ishani et al. (95), evaluated the long-term follow up of the MRFIT trial, and found that higher uric acid levels were associated with the development of end stage renal disease in men, even if this was reduced when individuals with baseline CKD (estimated GFR <60 mL/min per 1.73 m^2 or proteinuria) were excluded. This finding suggests that uric acid may be a marker of diminished kidney function rather than a direct cause of incipient kidney disease.

Nevertheless, strong evidence in favor of the hypothesis that elevated SUA itself contributes to the development of kidney disease has recently been published. A study of 21,475 healthy participants who were followed-up prospectively for a median of seven years were analyzed to examine the association between SUA levels and incidental kidney disease. The authors concluded that slightly elevated SUA levels independently increased the risk of new-onset kidney disease by 26%, even after adjusting for several potential confounding factors, including baseline GFR (11). In addition, in the ARIC and the CHS trials, conducted on over 13,000 participants with normal kidney function, the fully adjusted model showed a 7% increased risk for incidental kidney disease associated with each 1 mg/dL increase in baseline SUA levels (97). All things considered, SUA may induce kidney damage both directly and indirectly by promoting other well-known mechanisms of renal damage.

Lowering SUA for cardio-renal protection?

Despite the relatively large number of publications in the literature concerning the pathogenetic role of SUA in the development of CV and renal disease, to date, only a few, underpowered studies have investigated the effect of pharmacological reduction of SUA. Following treatment to lower serum urate, there have been reports of improvement in blood pressure control and delay in the progression of kidney damage (98, 99). The impact of allopurinol, the most commonly used urate-lowering drug, on the risk of mortality was analyzed in a population of 9,924 hyperuricemic veterans (100). In the incident allopurinol users, this treatment was associated with an almost 25% lower risk of all-cause mortality as compared to non-users. Randomized studies have shown improvements in blood-pressure control (17), CV damage (101) and slowing CKD progression (102) following serum urate lowering with allopurinol. However, most were short-term, small sized, single-center studies. In the only study with an adequate fol-

low up of 24 months, Goicoechea (103) showed how allopurinol treatment slows the progression of renal disease, and decreases inflammation and the risk of CV events and hospitalization.

It remains unclear, however, whether these benefits are entirely the results of the urate-lowering effect of allopurinol or of other beneficial effects of the drug caused by its action on XO activity such as improvement of endothelial dysfunction (104).

Nevertheless, new findings suggest that the observed benefits are more likely due to the reduction of uric acid per se than to the specific treatment strategy that is used. In a post hoc analysis of 1,342 patients with type 2 diabetes mellitus and nephropathy participating in the RENAAL trial, losartan treatment resulted in a reduction of SUA levels as compared to placebo, and a significantly lower risk for renal events (105). The effect of losartan on SUA explained approximately 20% of its renoprotective effect. These data confirm and extend previous reports from the LIFE study indicating a linear relationship between the losartan-associated reduction in SUA and the incidence of CV events.

The CV and renal protective effect that was observed by administering losartan could, at least in part, be due to its uricosuric action. In fact, losartan increases urate excretion by inhibiting URAT 1 mediated tubular reabsorption within the kidney (106). Moreover, URAT 1, a member of the organic anion transporter superfamily, has recently been shown to be expressed not only in the proximal tubule cells, but also in human aortic VSMCs (107). Therefore, one could speculate that losartan may exert its protective effect by preventing urate from entering the VSMCs, thus reducing cell proliferation and MCP-1 expression. Further prospective studies are clearly needed to confirm these interesting findings.

■ CONCLUSIONS

Several studies suggest that increased SUA is an independent predictor of CV and renal events and that it may be implicated in

the development of CV and renal damage. Preliminary data also suggest that pharmacological reduction of SUA may confer CV and renal protection. Further studies are needed to confirm the possible role of SUA as a surrogate end point of treatment.

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