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ABSTRACT

During the last century, there has been an increasing prevalence of hyperuricaemia noted in many populations. While uric acid is usually discussed in the context of gout, hyperuricaemia is also associated with hypertension, chronic kidney disease, hypertriglyceridaemia, obesity, atherosclerotic heart disease, metabolic syndrome, and type 2 diabetes. Here we review the connection between hyperuricaemia and cardiovascular, kidney and metabolic diseases. Contrary to the popular view that uric acid is an inert metabolite of purine metabolism, recent studies suggest serum uric acid may have a variety of pro-inflammatory, pro-oxidative and vasoconstrictive actions that may contribute to cardiometabolic diseases. Hyperuricaemia is a predictive factor for the development of hypertension, metabolic syndrome, type 2 diabetes, coronary artery disease, left ventricular hypertrophy, atrial fibrillation, myocardial infarction, stroke, heart failure and chronic kidney disease. Treatment with uric acid-lowering therapies has also been found to improve outcomes in patients with hypertension and kidney disease, in some but not all studies. In conclusion, uric acid is emerging as a potentially treatable risk factor for cardiometabolic diseases, and more clinical trials investigating the potential benefit of lowering serum uric acid are recommended in individuals with hyperuricaemia with and without deposition and concomitant hypertension, metabolic syndrome or chronic kidney disease.

Keywords: Allopurinol, Febuxostat, Hypertension, Hyperuricaemia, Metabolic syndrome, Type 2 diabetes

1. Introduction

Hyperuricaemia refers to an abnormally high concentration of uric acid in serum [1], typically defined as >7 mg/dL (416 μmol/L) in men and >6 mg/dL in women [2]. Mean serum uric acid has increased progressively over the last century in many populations [3]. In recent years, the US National Health and Nutrition Examination Survey (NHANES) has been the main source of epidemiological data on hyperuricaemia in Western countries (Table 1).[1] In the 2009–2010 analysis, the US adult population age-adjusted prevalence of hyperuricaemia was 19.3% [4]. Hyperuricaemia prevalence increases with age and is higher in men than premenopausal women [4-9], as oestrogen increases urate excretion by the kidneys [10]. The prevalence of hyperuricaemia is increasing over time [6,8,9,11,12] and according to NHANES data, increased significantly in the US from 19% in 1988–1994 to 21.5% in 2007–2008 [6]. In coastal regions of Eastern China, the prevalence of hyperuricaemia was estimated at 13% in 2008, while it was thought to be absent in the 1980s [9].

Hyperuricaemia is usually discussed in the context of gout, but it is increasingly recognised that serum uric acid values >6.5 mg/dL or 7.0 mg/dL in men and postmenopausal women and >6.0 mg/dL in premenopausal women are clinically relevant markers of other diseases [1,6,12,13]. Moreover, only 12% of individuals with

[1] **Abbreviations:** CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; EPIC, European Prospective Investigation into Cancer and Nutrition; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HOMA, homeostatic model assessment; HOMA-IR, homeostatic model assessment of insulin resistance; MCP-1, monocyte chemoattractant protein 1; NHANES, National Health and Nutrition Examination Survey.

serum uric acid between 7.0 mg/dL and 7.9 mg/dL develop gout [14,15], leading to the suggestion that uric acid-lowering medical interventions are unwarranted for asymptomatic hyperuricaemia unless an episode of gout occurs [1,15].

However, hyperuricaemia is not only associated with gout, but also with a variety of cardiometabolic diseases, including hypertension, chronic kidney disease (CKD), hypertriglyceridaemia, obesity, atherosclerotic heart disease, and metabolic syndrome [1]. Recently, a variety of studies have suggested that hyperuricaemia may be a risk factor for these conditions [12,16]. Here we critically review the relationship and discuss the pros and cons of therapeutic intervention based on the current studies.

2. Uric acid metabolism and biological activity

Uric acid is produced by xanthine oxidase [17] and is the final product of purine catabolism; it is excreted primarily in the urine and faeces [12,16]. Serum uric acid is affected by diets rich in purines and fructose, and is also produced during the degradation of nucleic acids (DNA and RNA) as well as ATP (such as may occur with increased cell turnover or muscle breakdown). As the kidney is a major site of excretion, a reduction in kidney function may also lead to a secondary increase in serum uric acid. Hormones such as estrogen can increase urate excretion, accounting for the lower levels of serum uric acid in premenopausal women. Other conditions, such as renal vasoconstriction in hypertension and insulin resistance, have also been thought to reduce urate excretion. Genetic polymorphisms in urate transport, especially SLC2A9 that regulates Glut9, can also influence serum urate levels. Genome-wide association

studies have identified SLC2A9 and other transporters as accounting for approximately 6% of the variance in serum uric acid levels [18,19].

Classically the association of hyperuricaemia with cardiometabolic diseases was thought to be due to the effects of diet, obesity and insulin resistance, renal disease, and as a consequence, serum uric acid was thought to not have a role in these conditions [15,20,21]. Indeed, some studies have suggested uric acid may be beneficial in cardiovascular diseases and function as an antioxidant [22].

However, more recent studies suggest that soluble uric acid may have a wide variety of pro-inflammatory effects. For example, uric acid has pro-oxidant effects in the intracellular environment as its production generates reactive oxygen species, which may cause oxidative stress [12,16] and because it can stimulate the production of NADPH oxidase [20]. Uric acid has a variety of cellular effects, including stimulation of growth factors, stimulation of cyclo-oxygenase 2 and thromboxane production, stimulation of chemokines (such as monocyte chemoattractant protein-1) and C-reactive protein, and increasing platelet activity and turnover [12,16,23-25]. Uric acid also activates the renin-angiotensin system by both stimulating plasma renin activity and renal renin expression, as well as by activating the intrarenal angiotensin system [26].

These effects have been shown to be responsible for inducing many aspects of cardiometabolic disease. Thus, experimental hyperuricaemia has been shown to induce systemic hypertension through vasoconstriction driven by the prooxidant effects of uric acid on vascular smooth muscle cells and inhibition of nitric oxide [27,28]. Likewise, uric acid has been shown to induce insulin resistance and gluconeogenesis via the

inhibition of hepatic AMP-activated protein kinase [29]. Fatty liver can be induced by experimental hyperuricaemia through the stimulation of lipogenesis and the inhibition of fatty acid oxidation driven by the induction of uric acid-dependent mitochondrial oxidative stress [20,30,31]. CKD is driven primarily by the development of a hypertrophic afferent arteriole that impairs autoregulation and allows increased transmission of systemic blood pressure to the glomerulus [3]. Cardiac disease may be secondary to the effects of hyperuricaemia to stimulate the renin-angiotensin system and cause hypertension, but uric acid has also been found in atherosclerotic plaque [32].

3. Hyperuricaemia and hypertension

3.1. Hyperuricaemia in patients with hypertension

The connection between hyperuricaemia and hypertension has been known for over a century [33]. Hyperuricaemia is found in 25% of individuals with untreated hypertension and three-quarters of patients with malignant hypertension [34]. The prevalence of hyperuricaemia is higher in people with pronounced hypertension [35]. Hyperuricaemia is associated with an increased risk of uncontrolled hypertension [36,37] and is associated with resistance to therapy [38].

3.2. Hyperuricaemia as a risk factor for hypertension

The association of hyperuricaemia with hypertension is independent of the traditional cardiovascular risk factors, including age, obesity, hypercholesterolaemia, hypertriglyceridaemia, low high-density lipoprotein (HDL) cholesterol, diabetes, family

history of hypertension, smoking and alcohol consumption [39]. In a meta-analysis of 18 prospective studies that included 55,607 participants with normal blood pressure at onset, hyperuricaemia was associated with an increased risk of incident hypertension (Table 2) [40]. Another meta-analysis of 25 prospective and retrospective studies (N = 97,824) concluded that hyperuricaemia was a predictive factor for developing hypertension, independently of sex and ethnicity (Asian vs non-Asian; Table 2) [41].

Hyperuricaemia may also be involved in the development of preeclampsia. Serum uric acid concentrations are higher in women with preeclampsia than in healthy pregnant women [42] and several physiological changes associated with pregnancy and preeclampsia can, in theory, lead to hyperuricaemia [42]. Nevertheless, the value of serum uric acid investigations in predicting maternal and foetal complications in women with preeclampsia was found to be low in a meta-analysis of 18 studies and 3,913 women (Table 2) [43].

Among 125 children (aged 6–18 years) recently diagnosed with primary hypertension, 89% had serum uric acid concentrations >5.5 mg/dL, while these levels occurred in only 30% of those diagnosed with secondary hypertension and in 0% of children with normal blood pressure [44]. Therefore, hyperuricaemia also correlates with hypertension in children.

4. Hyperuricaemia and metabolic disease

4.1. Prevalence of hyperuricaemia in metabolic diseases

Hyperuricaemia is also associated with metabolic syndrome and type 2 diabetes [45]. Epidemiological studies identified a positive correlation between serum uric acid concentrations and the prevalence of metabolic syndrome [46-50]. The prevalence of metabolic syndrome, based on NHANES 1988–1994 data, showed a stepwise increase from 18.9% in individuals with serum uric acid concentrations <6 mg/dL to 70.7% in those with serum uric acid concentration ≥10 mg/dL [46]. This association was independent of sex, age, alcohol consumption, body mass index and the presence of hypertension and diabetes. In addition, the prevalence of individual components of metabolic syndrome, including hyperglycaemia, hypertriglyceridaemia, low HDL cholesterol and hypertension, also increased with increasing serum uric acid levels, with the exception of abdominal obesity, which was slightly decreased in individuals with very high serum uric acid concentrations (≥10 mg/dL) [46]. In prospective observational studies, elevated serum uric acid concentrations have been found to predict the risk of developing metabolic syndrome and its individual components [51,52].

Several studies have examined the effect of sex on the association between elevated serum uric acid levels and the risk of developing metabolic syndrome. Higher levels of serum uric acid were significantly associated with a higher risk of developing metabolic syndrome in a prospective observational study of healthy men (N = 8,429) and women (N = 1,260) who were followed for a mean of 5.5 years [53]. In a meta-analysis of seven prospective cohort studies that included 23,081 men and 12,195 women, the incidence of metabolic syndrome increased by approximately 5% in men and 9% in women for every 1 mg/dL increase in serum uric acid concentration (Table 2) [54]. For an equivalent increase in uric acid concentrations, the risk of developing metabolic

syndrome was higher among women <52 years old than in males or older females (Table 2) [54]. In an analysis of 10,649 men and 12,696 women who participated in the Dongfeng-Tongji cohort study, the association between uric acid levels and the risk of developing metabolic syndrome was significantly stronger in women [47].

The link between uric acid levels and metabolic syndrome has also been reported in children [55]. In adolescents, the relationship between serum uric acid levels and metabolic syndrome is more complex. Elevated uric acid was predictive of developing metabolic syndrome in males but not in females in a study that included 5,748 individuals aged 10–15 years who were followed for a median of 7.2 years [56].

4.2. Hyperuricaemia as a risk factor for metabolic diseases

Elevated levels of uric acid were found to be associated with insulin resistance in women and in individuals with obesity, while there was no association in non-obese men in a study of 88 non-diabetic individuals without cardiovascular disease [57]. A number of studies have reported an increased risk of type 2 diabetes in individuals with elevated uric acid levels [52,58]. In addition, individual components of the metabolic syndrome, except dyslipidaemia, are more common in individuals with elevated uric acid and type 2 diabetes [59]. Several meta-analyses have produced estimates of the dose-response relationship (Table 2). In an early meta-analysis, which included 11 observational cohort studies and 42,834 participants, the authors concluded that the risk of developing type 2 diabetes is increased by 17% for each 1 mg/dL increment in serum uric acid concentration [58]. However, in a later meta-analysis of eight prospective cohort studies and 32,016 participants that employed a more rigorous methodology, the

risk of developing type 2 diabetes was reported to be increased by 6% for every 1 mg/dL increment in serum uric acid [60]. The association between uric acid levels and type 2 diabetes was independent of the presence of individual components of metabolic syndrome [60]. Furthermore, an analysis of data from the European Prospective Investigation into Cancer and Nutrition (EPIC)-InterAct study comprising 24,265 individuals aged 35–70 years, concluded that the risk of developing type 2 diabetes increases by 20% for every 1 mg/dL increase in uric acid concentration [61]. However, the results of instrumental multivariable analysis did not confirm this finding, casting doubt on the existence of a causal relationship between the two conditions [61].

5. Hyperuricaemia and cardiovascular disease

Epidemiological studies have examined the association between hyperuricaemia and cardiovascular disease. Earlier studies tended to conclude that elevated uric acid levels were a marker of cardiovascular risk and did not have any predictive value [5,62,63]. More recent studies found a significant association between hyperuricaemia and several cardiovascular conditions, which remained robust even after adjustment for potential confounders [64]. Increased serum uric acid levels are significantly associated with the presence and severity of coronary artery disease [65] and increased left ventricular size and atrial fibrillation in healthy and hypertensive individuals [66,67]. Increased serum uric acid concentrations is a risk factor for myocardial infarction, stroke [68], and heart failure [69]. The Brisighella heart study also reported a significant correlation between elevated serum uric acid levels and hypertension and atherosclerosis (including both increased carotid intima-media thickness and pulse wave velocity) [70]. Meta-analyses

reported that elevated serum uric acid conferred a modest, yet statistically significant, risk of stroke and death from stroke in both men and women [71], and that it is an independent risk factor for developing heart failure and adverse outcomes in patients with existing heart failure (Table 2) [72]. Hyperuricaemia also predicted one-year mortality in patients with acute heart failure [73] and adverse outcomes and death in patients with acute myocardial infarction [74,75]. In patients with chronic heart failure, increased serum uric acid levels demonstrated a significant association with diastolic dysfunction [76]. In particular, the prognostic value of elevated serum uric acid is associated with that of brain natriuretic peptide (BNP) [77], a common biomarker in patients with left ventricular dysfunction. The prognostic values of serum urate and BNP appear to be independent but the combined elevation of both biomarkers in the same subject is associated with the worst prognosis and can be used to monitor clinical evolution in patients with acute heart failure [77]. Elevated serum uric acid levels are also associated with the development of cardiac hypertrophy [78,79]. On the other hand, the results of a study conducted in 173 patients with normal uric acid concentrations, hyperuricaemia or gouty arthritis, indicate that gout is associated with left ventricular diastolic dysfunction, while the hyperuricaemia is not [80].

In addition to major cardiovascular disease, an increase in serum uric acid has been associated with both microvascular disease and peripheral artery disease. Coronary microvascular disease is suspected when there is the absence of a “myocardial blush” during coronary angiogram, and it is associated with hyperuricaemia and carries a higher one-year mortality following percutaneous intervention (PC) therapy of ST-elevation associated myocardial infarction compared to coronary artery disease in which

the myocardial blush is observed [81]. Abnormalities in coronary microcirculation have been described by Prasad et al. [82] in post-menopausal women and associated with hyperuricaemia and inflammation. An increase in serum urate levels has also been reported in patients with elevated calcium scores, with an independent link between asymptomatic hyperuricaemia and coronary artery calcification in the absence of overt cardiovascular disease [83]. An increased coronary calcium score has also been described in patients with hyperuricaemia and asymptomatic urate deposition at the joint level, and could explain the increased cardiovascular risk in patients with "symptomless gout" [84]. Finally, a longitudinal association has been described between serum uric acid levels and peripheral atherosclerosis including intra- and extra-cranial vascular system and peripheral vascular disease as estimated by transcranial Doppler, carotid ultrasound and ankle-brachial index measures [85]. The association was confirmed regardless of the presence of additional risk factors and after adjustment for the most important confounding variables.

6. Hyperuricaemia and chronic kidney disease

A large body of evidence links hyperuricaemia with the development of CKD. Studies in the general population have demonstrated that hyperuricaemia is an independent risk factor for the development of CKD [86-92]. Similarly, studies conducted in patients with type 1 [93] and type 2 diabetes [94] have shown that hyperuricaemia predicts the development of new-onset CKD in these populations. However, not all studies have demonstrated a significant association between elevated serum uric acid levels and the risk of incident CKD [95].

Several large-scale studies conducted in the general population have confirmed that hyperuricaemia predicts the development of end-stage kidney failure (CKD 5), a major clinical end-point [96,97], and that elevated uric acid levels during the first year following a kidney transplant procedure predict graft loss [98,99]. Recent evidence also implicates perioperative hyperuricaemia in the pathogenesis of acute kidney injury in patients undergoing cardiovascular surgery [67,100,101]. In addition, there is increasing evidence that even mild hyperuricaemia correlates with early kidney damage, as shown by albuminuria and kidney ultrasound abnormalities [102].

7. Uric acid-lowering drugs

7.1 Uric acid-lowering therapy in clinical practice

Current European guidelines for the management of gout recommend starting uric acid-lowering therapy at a low dose and titrating upwards until the target serum uric acid level is reached [103]. First, we would recommend reviewing the drugs the patient is taking that may increase serum uric acid, such as thiazides and loop diuretics, and to change them if there are no contraindications. Second, in subjects using modulators of the renin-angiotensin system, we would consider switching to drugs able to reduce serum uric acid independently of their involvement in blocking the action of angiotensin II [104].

For most subjects, uric acid-lowering drugs will necessitate the use of xanthine-oxidase inhibitors, such as allopurinol and febuxostat. The approved dose for allopurinol is between 100 and 900 mg/day in adults and up to 400 mg/day in children (10 to 20

mg/kg/day) [105] and is indicated to reduce urate/uric acid formation in conditions where the deposition has already occurred; its use in children is rarely recommended [105]. Lower doses are advisable in patients with renal or hepatic impairment [105]. Treatment with febuxostat, indicated in adults for the management of chronic hyperuricaemia in conditions where urate deposition has already occurred, should be started at 80 mg/day and increased to 120 mg/day if target serum uric acid levels of <6.0 mg/dL are not reached at the starting dose [106]. In patients with mild hepatic impairment, the recommended dose of febuxostat is 80 mg/day, but no dose adjustment is needed in patients with mild-to-moderate renal impairment (CrCl 30–89 mL/min) [106].

The approved starting dose of febuxostat in the USA is 40 mg/day, with an increase to 80 mg/day in those who do not achieve serum uric acid of <6 mg/dL; in patients with severe renal dysfunction, i.e., CKD 4 (CrCl 15–29 mL/min), the maximum daily dose should be limited to 40 mg/day [107].

In terms of direct comparison between classes of uric acid-lowering drugs, most of the reported effectiveness of treatment has been ascribed to xanthine-oxidase inhibitors [108], while the uricosuric agents are not universally available and are mostly recommended in combination with xanthine oxidase inhibitors or as a single treatment in patients where xanthine-oxidase inhibitors are not tolerated or are contraindicated. Febuxostat has been reported to be superior to allopurinol in patients with gout as far as the reduction in serum urate and the percentage of patients who achieve the goal for serum uric acid concentrations according to guidelines (<6 mg/dL or <5 mg/dL in patients with severe gout) [109]. As far as cardiovascular prevention, the evidence is

still a matter of debate, but supports some degree of cardiovascular prevention in patients treated with urate-lowering drugs, mainly xanthine-oxidase inhibitors with some differences between the different drugs (see below).

7.2 In hypertension

Several studies suggest that uric acid-lowering treatment may reduce blood pressure in hyperuricaemic people with hypertension, especially those who are young, have not had a longstanding history of hypertension, and have relatively preserved renal function. Allopurinol significantly reduced systolic and diastolic blood pressure in children and adolescents with newly diagnosed essential hypertension [110,111]. Significant reductions in systolic ($p = 0.0003$) and diastolic blood pressure ($p = 0.0007$) were also demonstrated in a randomised, placebo-controlled study of 60 adolescents with prehypertension treated with either allopurinol or probenecid (a uricosuric) compared with placebo [112]. An analysis of data from elderly patients with hypertension from the UK Clinical Practice Research Datalink, which included 365 patients who received allopurinol and 6,678 controls, found that uric acid-lowering treatment was associated with significant reductions in both systolic and diastolic blood pressure ($p < 0.001$) [113]. In addition, studies suggest that if blood pressure is in the normal range (<140/90 mm Hg), treatment may not result in significant lowering of blood pressure [114, 115].

The efficacy of another xanthine oxidase inhibitor, febuxostat, was evaluated in a phase II, randomised, double-blind, placebo-controlled study of 121 patients with hypertension and hyperuricaemia [116]. At week 6, there were no significant differences between the febuxostat and the placebo group in the primary endpoint of 24-

hour mean ambulatory systolic blood pressure. Diastolic blood pressure was also not significantly different between the groups. However, a planned subgroup analysis of patients with normal kidney function revealed that, in this cohort, systolic blood pressure was significantly reduced after 6 weeks of treatment with febuxostat (p = 0.049) [116]. In a recent study in patients with stage 3 CKD, febuxostat at a dose of 40 mg per day had no effect on blood pressure over 2 years of treatment [117].

A meta-analysis of both prospective and retrospective studies, which evaluated the effects of 4 weeks' allopurinol treatment on blood pressure and included 10 studies and 738 patients, showed that allopurinol significantly reduced systolic and diastolic pressure compared with the control group (Table 2) [118]. This effect was lower than in other studies [110,111]; however, the age of populations analysed differed [118].

7.3 In metabolic disease

The adverse effects of hyperuricaemia can be partly prevented by lowering serum uric acid levels. Allopurinol was shown to lower uric acid and improve insulin resistance and systemic inflammation in a prospective, randomised study of 73 individuals with asymptomatic hyperuricaemia who received either allopurinol 300 mg per day or no treatment for three months (N = 73) [119]. Similarly, another study reported that treatment with febuxostat decreased uric acid levels and improved insulin resistance in patients with gout [120]. In a randomised, controlled study of 74 adult men who received 200 g of fructose for 2 weeks, treatment with allopurinol was shown to prevent increases in blood pressure and the incidence of newly diagnosed metabolic syndrome compared with men who did not receive allopurinol, while no effect on homeostatic

model assessment (HOMA) indices or fasting plasma triglyceride levels could be detected [121]. Furthermore, in patients with non-alcoholic fatty liver disease, which is part of the metabolic syndrome complex, allopurinol for three months significantly improved the serum levels of alanine and aspartate transaminases, cholesterol and triglycerides compared with placebo [122].

7.4 In cardiovascular disease

Controlling uric acid levels with appropriate drugs can be beneficial in patients with cardiovascular disease. A retrospective study reported a decreased incidence of stroke and cardiovascular events in hypertensive adults treated with allopurinol [123]. Treatment with allopurinol improved blood flow and peripheral vasodilator capacity in patients with chronic heart failure in two placebo-controlled studies [124]. Another randomised, placebo-controlled study reported improvement in endothelial dysfunction with allopurinol in patients with chronic heart failure [125]. Similarly, a randomised, placebo-controlled study reported that high doses of allopurinol might decrease mortality in patients with coronary artery disease by reducing vascular oxidative stress and improving endothelial dysfunction [126]. In addition, a systematic review and meta-analysis reported that treatment with xanthine oxidase inhibitors improved endothelial function and circulating oxidative stress markers in patients at risk of cardiovascular disease [127]. Nevertheless, not all studies have found lowering uric acid to provide cardiovascular benefit. Recent studies suggest this may relate to the duration a subject received allopurinol, as there appears to be a stepwise reduction in risk for both

myocardial infarction and stroke the longer the therapy in older subjects, with optimal benefit requiring two years or more duration [128,129].

On the other hand, benzbromarone, a uricosuric that does not affect xanthine oxidase, was not associated with improvements in haemodynamic parameters, including left ventricular ejection fraction, heart rate and blood pressure, in a randomised, double-blind, placebo-controlled study conducted in 82 patients with chronic heart failure [130]. Nevertheless, treatment with benzbromarone was shown to significantly reduce serum uric acid concentrations and improve fasting insulin and HOMA-IR [130]. The superiority of xanthine oxidase inhibitors can be explained by their multiple mechanisms of action that involves a reduction in serum uric acid levels, a decrease in vascular oxidative stress associated with a decline in the intracellular levels of uric acid. This is not the case for any uricosuric agent (probenecid, benzbromarone and lesinurad) that only affects urate transport without any effect on the pro-oxidative system.

The Febuxostat for Cerebral and Cardiorenovascular Events Prevention Study (FREED) randomised controlled trial [131], recently published in the European Heart Journal, revealed that treatment with febuxostat lowered the composite endpoint of cerebral, cardiovascular, and renal events by 25% in elderly patients with hyperuricaemia. Interestingly, a population-based cohort study recently found a modestly decreased risk for heart failure exacerbation in gout patients who were treated with febuxostat compared with allopurinol [132]. In addition, results of the FEATHER study carried out in patients with stage 3 CKD [117] have reported a lesser rate of major adverse cardiovascular events in patients treated with febuxostat in comparison with placebo (11.7% vs 28.3%). Both studies were carried out with low doses of febuxostat, thereby

supporting a favourable interaction between the reduction in serum urate level and the selectivity of xanthine oxidase inhibition for the prevention of cardiovascular disease. The Randomized Trial of Effect of Urate-Lowering Agent Febuxostat in Chronic Heart Failure Patients with Hyperuricaemia (LEAF-CHF) is currently underway to investigate the potential additional benefit of febuxostat in heart failure in a prospective manner [133].

7.5 In kidney disease

Uric acid-lowering treatment with allopurinol or febuxostat has been reported to be effective in the management of CKD. In asymptomatic people with hyperuricaemia, treatment with allopurinol resulted in significantly greater improvements in both endothelial function and estimated GFR (eGFR) compared with placebo [134]. Similarly, patients with hypertension and asymptomatic hyperuricaemia treated with febuxostat have been shown to experience greater improvements in eGFR and greater suppression of the renin-angiotensin-aldosterone system than controls [135]. In studies of patients with CKD, allopurinol slowed the progression of disease, reduced the likelihood of kidney failure and improved measures of cardiovascular risk [136-138]. In one study, higher doses of allopurinol were associated with reduced risk of kidney failure [137], while in another study, the achievement of target uric acid concentrations of <6mg/dL reduced the risk of kidney disease progression by 37% [136]. Treatment with febuxostat has been shown to reduce the progression of eGFR decline in patients with CKD [139]. While some trials have not been able to show renal protection, the primary reason appears to be because there was no progression of kidney disease in the

control group over the time period of the trial. To date, the largest prospective randomized trial in patients with stage 3 CKD showed that, compared with placebo, febuxostat did mitigate the decline in kidney function through lowering asymptomatic hyperuricaemia, but only in non-proteinuric patients with a rather high eGFR (52ml/min) [117]. The protective effect of febuxostat on the kidney was further confirmed in the FREED study (N = 1,070) in which the secondary endpoint of renal impairment was significantly lower in the febuxostat group than the allopurinol group. A recent meta-analysis looking at 1,317 patients studied in 11 trials showed that other than its urate-lowering effect, febuxostat presented a reno-protective effect in CKD patients [140].

However, there are studies where lowering uric acid has been reported to carry no benefit in hyperuricaemic subjects on the progression of CKD [117]. In many of these trials, however, the control group failed to show progression of their kidney disease over the time period studied [141]. Indeed, in trials in which there was a significant progression in the control group, the use of xanthine oxidase inhibitors is uniformly protective. This has led to the suggestion that uric acid-lowering therapy should be recommended for hyperuricaemic individuals with CKD stage 3 or higher who are showing signs of active renal progression [141]. Nevertheless, additional research, particularly large randomised controlled studies, is necessary to confirm these findings and further elucidate the precise nature of the renoprotective effects conferred by uric acid-lowering treatments.

8 Conclusions

Contrary to the belief that uric acid is an inert metabolite, uric acid may be an active participant in a complex network of pathological processes, including hypertension, insulin resistance, cardiovascular and CKD (Fig. 1). While more clinical trials are needed to determine whether specific uric acid-lowering therapy may benefit cardiometabolic disease, there appears to be enough evidence to warrant measuring serum uric acid for its predictive risks. For those people with hyperuricaemia, we recommend initiating lifestyle changes including dietary restriction of high purine foods and fructose-containing sugars. The decision of whether to treat individuals with hyperuricaemia with and without deposition and concomitant hypertension, metabolic syndrome or CKD with uric acid-lowering drugs remains open, but if done should involve a discussion with the patient on the benefits versus risks of treatment. This is especially important given that lowering uric acid is currently not approved for the treatment of cardiometabolic disease and because of the potential adverse effects of treatment. Most importantly, further research, particularly large randomised controlled trials, are necessary to address the effects of uric acid-lowering therapies on clinical outcomes.

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Declaration of Competing Interest

Claudio Borghi is a consultant for Menarini Corporate, Sanofi, Novartis, Grunenthal and Takeda, and has taken part in Boards of speakers for Servier, Menarini, Novartis, Roche, MSD, Takeda, Astellas, Tejin, Berlin-Chemie and Recordati.

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Richard J. Johnson has patents and patent applications related to the role of sugar and/or uric acid in metabolic diseases, and also has equity with two startup companies (XORT Therapeutics and Colorado Research Partners LLC) interested in developing inhibitors of uric acid and fructose metabolism. Dr Johnson has also received funding from the NIH, DOD, VA, and Danone Research Foundation. He has also received honoraria from Horizon Pharmaceuticals and Astra Zeneca.

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Empar Lurbe has no conflict of interest to declare.

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Author contributions

Claudio Borghi contributed to the coordination of the scientific panel, review of the literature and preparation of the manuscript. Enrico Agabiti-Rosei contributed to formulating review questions and read and approved drafts of the manuscript. Richard J. Johnson contributed to formulating review questions and read and approved drafts of the manuscript. Jan T Kielstein contributed to formulating review questions, read, revised and approved drafts of the manuscript. Empar Lurbe contributed to formulating review questions and literature review and read and approved drafts of the manuscript. Giuseppe Mancia contributed to formulating review questions and read and approved drafts of the manuscript. Josep Redon contributed to formulating review questions and

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References

[1] Becker MA. Hyperuricemia. In: Lang F, editor. Encyclopedia of Molecular Mechanisms of Disease. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009. p. 956.

[2] Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. Curr Opin Rheumatol 2014;26:186-91.

[3] Sanchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, et al. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. Kidney Int 2005;67:237-47.

[4] Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS One 2012;7:e50046.

[5] Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med 1999;131:7-13.

[6] Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum 2011;63:3136-41.

[7] Chuang SY, Lee SC, Hsieh YT, Pan WH. Trends in hyperuricemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993-1996 to 2005-2008. Asia Pac J Clin Nutr 2011;20:301-8.

[8] Trifiro G, Morabito P, Cavagna L, Ferrajolo C, Pecchioli S, Simonetti M, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005-2009: a nationwide population-based study. Ann Rheum Dis 2013;72:694-700.

[9] Miao Z, Li C, Chen Y, Zhao S, Wang Y, Wang Z, et al. Dietary and lifestyle changes associated with high prevalence of hyperuricemia and gout in the Shandong coastal cities of Eastern China. J Rheumatol 2008;35:1859-64.

[10] Nicholls A, Snaith ML, Scott JT. Effect of oestrogen therapy on plasma and urinary levels of uric acid. Br Med J 1973;1:449-51.

[11] Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. Semin Nephrol 2011;31:410-9.

[12] Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183-90.

[13] Desideri G, Castaldo G, Lombardi A, Mussap M, Testa A, Pontremoli R, et al. Is it time to revise the normal range of serum uric acid levels? Eur Rev Med Pharmacol Sci 2014;18:1295-306.

[14] Langford HG, Blaufox MD, Borhani NO, Curb JD, Molteni A, Schneider KA, et al. Is thiazide-produced uric acid elevation harmful? Analysis of data from the Hypertension Detection and Follow-up Program. Arch Intern Med 1987;147:645-9.

[15] Paul BJ, Anoopkumar K, Krishnan V. Asymptomatic hyperuricemia: is it time to intervene? Clin Rheumatol 2017;36:2637-44.

[16] Kanellis J, Kang DH. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. Semin Nephrol 2005;25:39-42.

[17] Baillie JK, Bates MG, Thompson AA, Waring WS, Partridge RW, Schnopp MF, et al. Endogenous urate production augments plasma antioxidant capacity in healthy lowland subjects exposed to high altitude. Chest 2007;131:1473-8.

[18] Kolz M, Johnson T, Sanna S, Teumer A, Vitart V, Perola M, et al. Meta-analysis of 28,141 individuals identifies common variants within five new loci that influence uric acid concentrations. PLoS Genet 2009;5:e1000504.

[19] Yang Q, Kottgen A, Dehghan A, Smith AV, Glazer NL, Chen MH, et al. Multiple genetic loci influence serum urate levels and their relationship with gout and cardiovascular disease risk factors. Circ Cardiovasc Genet 2010;3:523-30.

[20] Lanaspa MA, Sanchez-Lozada LG, Choi YJ, Cicerchi C, Kanbay M, Roncal-Jimenez CA, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. J Biol Chem 2012;287:40732-44.

[21] Woods HF, Eggleston LV, Krebs HA. The cause of hepatic accumulation of fructose 1-phosphate on fructose loading. Biochem J 1970;119:501-10.

[22] Maxwell SR, Thomason H, Sandler D, Leguen C, Baxter MA, Thorpe GH, et al. Antioxidant status in patients with uncomplicated insulin-dependent and non-insulin-dependent diabetes mellitus. Eur J Clin Invest 1997;27:484-90.

[23] Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, et al. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension 2003;41:1287-93.

[24] Mustard JF, Murphy EA, Ogryzlo MA, Smythe HA. Blood coagulation and platelet economy in subjects with primary gout. Can Med Assoc J 1963;89:1207-11.

[25] Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem 1991;266:8604-8.

[26] Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. J Hypertens 2010;28:1234-42.

[27] Sanchez-Lozada LG, Soto V, Tapia E, Avila-Casado C, Sautin YY, Nakagawa T, et al. Role of oxidative stress in the renal abnormalities induced by experimental hyperuricemia. Am J Physiol Renal Physiol 2008;295:F1134-41.

[28] Sanchez-Lozada LG, Tapia E, Lopez-Molina R, Nepomuceno T, Soto V, Avila-Casado C, et al. Effects of acute and chronic L-arginine treatment in experimental hyperuricemia. Am J Physiol Renal Physiol 2007;292:F1238-44.

[29] Cicerchi C, Li N, Kratzer J, Garcia G, Roncal-Jimenez CA, Tanabe K, et al. Uric acid-dependent inhibition of AMP kinase induces hepatic glucose production in diabetes and starvation: evolutionary implications of the uricase loss in hominids. FASEB J 2014;28:3339-50.

[30] Lanaspa MA, Cicerchi C, Garcia G, Li N, Roncal-Jimenez CA, Rivard CJ, et al. Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver. PLoS One 2012;7:e48801.

[31] Lanaspa MA, Sanchez-Lozada LG, Cicerchi C, Li N, Roncal-Jimenez CA, Ishimoto T, et al. Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver. PLoS One 2012;7:e47948.

[32] Felici C, Ciari I, Terzuoli L, Porcelli B, Setacci C, Giubbolini M, et al. Purine catabolism in advanced carotid artery plaque. Nucleosides Nucleotides Nucleic Acids 2006;25:1291-4.

[33] Wang S, Shu Z, Tao Q, Yu C, Zhan S, Li L. Uric acid and incident chronic kidney disease in a large health check-up population in Taiwan. Nephrology 2011;16:767-76.

[34] Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. N Engl J Med 1966;275:457-64.

[35] Juraschek SP, Kovell LC, Miller ER, Gelber AC. Dose-response association of uncontrolled blood pressure and cardiovascular disease risk factors with hyperuricemia and gout. PLoS One 2013;8:e56546.

[36] Cho J, Kim C, Kang DR, Park JB. Hyperuricemia and uncontrolled hypertension in treated hypertensive patients: K-MetS Study. Medicine (Baltimore) 2016;95:e4177.

[37] Cicero AF, Rosticci M, Fogacci F, Grandi E, D'Addato S, Borghi C. High serum uric acid is associated to poorly controlled blood pressure and higher arterial stiffness in hypertensive subjects. Eur J Intern Med 2017;37:38-42.

[38] Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, et al. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: Results from the EURIKA study. Int J Cardiol 2016;218:83-8.

[39] Nagahama K, Inoue T, Iseki K, Touma T, Kinjo K, Ohya Y, et al. Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. Hypertens Res 2004;27:835-41.

[40] Grayson PC, Kim SY, LaValley M, Choi HK. Hyperuricemia and incident hypertension: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2011;63:102-10.

[41] Wang J, Qin T, Chen J, Li Y, Wang L, Huang H, et al. Hyperuricemia and risk of incident hypertension: a systematic review and meta-analysis of observational studies. PLoS One 2014;9:e114259.

[42] Martin AC, Brown MA. Could uric acid have a pathogenic role in pre-eclampsia? Nat Rev Nephrol 2010;6:744-8.

[43] Thangaratinam S, Ismail KM, Sharp S, Coomarasamy A, Khan KS. Accuracy of serum uric acid in predicting complications of pre-eclampsia: a systematic review. BJOG 2006;113:369-78.

[44] Feig DI, Johnson RJ. Hyperuricemia in childhood primary hypertension. Hypertension 2003;42:247-52.

[45] Boyle JA, McKiddie M, Buchanan KD, Jasani MGH, Jackson IM, Buchanan WW. Dietes mellitus and gout. Blood sugar and plasma insulin responses to oral glucose in normal weight, overweight, and gouty patients. Ann Rheum Dis 1969;28:374-8.

[46] Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals with hyperuricemia. Am J Med 2007;120:442-7.

[47] Dai X, Yuan J, Yao P, Yang B, Gui L, Zhang X, et al. Association between serum uric acid and the metabolic syndrome among a middle- and old-age Chinese population. Eur J Epidemiol 2013;28:669-76.

[48] Nejatinamini S, Ataie-Jafari A, Qorbani M, Nikoohemat S, Kelishadi R, Asayesh H, et al. Association between serum uric acid level and metabolic syndrome components. Journal of diabetes and metabolic disorders 2015;14:70.

[49] Borghi C, Rosei EA, Bardin T, Dawson J, Dominiczak A, Kielstein JT, et al. Serum uric acid and the risk of cardiovascular and renal disease. J Hypertens 2015;33:1729-41.

[50] He SJ, Chan C, Xie ZD, Shi D, Hu XB, Li HY, et al. The relationship between serum uric acid and metabolic syndrome in premenopausal and postmenopausal women in the Jinchang Cohort. Gynecol Endocrinol 2017;33:141-4.

[51] Tian Y, Chen K, Xie Z, Fang Y, Wang H, Nie Y, et al. The association between serum uric acid levels, metabolic syndrome and cardiovascular disease in middle aged and elderly Chinese: results from the DYSlipidemia International Study. BMC Cardiovasc Disord 2015;15:66.

[52] Oda E. Serum uric acid is an independent predictor of metabolic syndrome in a Japanese health screening population. Heart Vessels 2014;29:496-503.

[53] Sui X, Church TS, Meriwether RA, Lobelo F, Blair SN. Uric acid and the development of metabolic syndrome in women and men. Metabolism 2008;57:845-52.

[54] Liu Z, Que S, Zhou L, Zheng S. Dose-response relationship of serum uric acid with metabolic syndrome and non-alcoholic fatty liver disease incidence: a meta-analysis of prospective studies. Sci Rep 2015;5:14325.

[55] Sun D, Li S, Zhang X, Fernandez C, Chen W, Srinivasan SR, et al. Uric acid is associated with metabolic syndrome in children and adults in a community: the Bogalusa Heart Study. PLoS One 2014;9:e89696.

[56] Sun HL, Pei D, Lue KH, Chen YL. Uric acid levels can predict metabolic syndrome and hypertension in adolescents: a 10-year longitudinal study. PLoS One 2015;10:e0143786.

[57] Elizalde-Barrera CI, Estrada-Garcia T, Lozano-Nuevo JJ, Garro-Almendaro AK, Lopez-Saucedo C, Rubio-Guerra AF. Serum uric acid levels are associated with homeostasis model assessment in obese nondiabetic patients: HOMA and uric acid. Ther Adv Endocrinol Metab 2017;8:141-6.

[58] Kodama S, Saito K, Yachi Y, Asumi M, Sugawara A, Totsuka K, et al. Association between serum uric acid and development of type 2 diabetes. Diabetes Care 2009;32:1737-42.

[59] Marotta T, Liccardo M, Schettini F, Verde F, Ferrara AL. Association of hyperuricemia with conventional cardiovascular risk factors in elderly patients. J Clin Hypertens 2015;17:27-32.

[60] Lv Q, Meng XF, He FF, Chen S, Su H, Xiong J, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. PLoS One 2013;8:e56864.

[61] Sluijs I, Holmes MV, van der Schouw YT, Beulens JW, Asselbergs FW, Huerta JM, et al. A Mendelian randomization study of circulating uric acid and type 2 diabetes. Diabetes 2015;64:3028-36.

[62] Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) Study. Ann Epidemiol 2000;10:136-43.

[63] Wheeler JG, Juzwishin KD, Eiriksdottir G, Gudnason V, Danesh J. Serum uric acid and coronary heart disease in 9,458 incident cases and 155,084 controls: prospective study and meta-analysis. PLoS Med 2005;2:e76.

[64] Borghi C, Rodriguez-Artalejo F, De Backer G, Dallongeville J, Medina J, Guallar E, et al. The association between blood pressure and lipid levels in Europe: European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice. J Hypertens 2016;34:2155-63.

[65] Sinan Deveci O, Kabakci G, Okutucu S, Tulumen E, Aksoy H, Baris Kaya E, et al. The association between serum uric acid level and coronary artery disease. Int J Clin Pract 2010;64:900-7.

[66] Chao TF, Hung CL, Chen SJ, Wang KL, Chen TJ, Lin YJ, et al. The association between hyperuricemia, left atrial size and new-onset atrial fibrillation. Int J Cardiol 2013;168:4027-32.

[67] Liu Y, Tan N, Chen J, Zhou Y, Chen L, Chen S, et al. The relationship between hyperuricemia and the risk of contrast-induced acute kidney injury after percutaneous coronary intervention in patients with relatively normal serum creatinine. Clinics 2013;68:19-25.

[68] Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke 2006;37:1503-7.

[69] Krishnan E. Hyperuricemia and incident heart failure. Circ Heart Fail 2009;2:556-62.

[70] Cicero AF, Salvi P, D'Addato S, Rosticci M, Borghi C. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. J Hypertens 2014;32:57-64.

[71] Li M, Hou W, Zhang X, Hu L, Tang Z. Hyperuricemia and risk of stroke: a systematic review and meta-analysis of prospective studies. Atherosclerosis 2014;232:265-70.

[72] Huang H, Huang B, Li Y, Huang Y, Li J, Yao H, et al. Uric acid and risk of heart failure: a systematic review and meta-analysis. Eur J Heart Fail 2014;16:15-24.

[73] Okazaki H, Shirakabe A, Kobayashi N, Hata N, Shinada T, Matsushita M, et al. Are atherosclerotic risk factors associated with a poor prognosis in patients with hyperuricemic acute heart failure? The evaluation of the causal dependence of acute heart failure and hyperuricemia. Heart Vessels 2017;32:436-45.

[74] Shimizu T, Yoshihisa A, Kanno Y, Takiguchi M, Sato A, Miura S, et al. Relationship of hyperuricemia with mortality in heart failure patients with preserved ejection fraction. Am J Physiol Heart Circ Physiol 2015;309:H1123-9.

[75] Piepoli MF, MD, PhD, Corrà U, MD, Doni F et al, Increased serum uric acid level predicts poor prognosis in mildly severe chronic heart failure with reduced ejection fraction. An analysis from the MECKI score research group. Eur J Intern Med, 2019

[76] Cicoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, et al. Elevated serum uric acid levels are associated with diastolic dysfunction in patients with dilated cardiomyopathy. Am Heart J 2002;143:1107-11.

[77] Sakai H, Tsutamoto T, Tsutsui T, Tanaka T, Ishikawa C, Horie M. Serum level of uric acid, partly secreted from the failing heart, is a prognostic marker in patients with congestive heart failure. Circ J 2006;70:1006-11.

[78] Cuspidi C, Facchetti R, Bombelli M, Sala C, Tadic M, Grassi G, et al. Uric acid and new onset left ventricular hypertrophy: findings from the PAMELA population. Am J Hypertens 2017;30:279-85.

[79] Viazzi F, Parodi D, Leoncini G, Parodi A, Falqui V, Ratto E, et al. Serum uric acid and target organ damage in primary hypertension. Hypertension 2005;45:991-6.

[80] Lin JC, Lin CL, Chen MC, Chang PJ, Chang ST, Chung CM, et al. Gout, not hyperuricemia alone, impairs left ventricular diastolic function. Arthritis Res Ther 2015;17:323.

[81] Basar N, Sen N, Ozcan F, Erden G, Kanat S, Sokmen E, et al. Elevated serum uric acid predicts angiographic impaired reperfusion and 1-year mortality in ST-segment elevation myocardial infarction patients undergoing percutaneous coronary intervention. J Investig Med 2011;59:931-7.

[82] Prasad M, Matteson EL, Herrmann J, Gulati R, Rihal CS, Lerman LO, et al. Uric acid is associated with inflammation, coronary microvascular dysfunction, and adverse outcomes in postmenopausal women. Hypertension 2017;69:236-42.

[83] Kim H, Kim SH, Choi AR, Kim S, Choi HY, Kim HJ, et al. Asymptomatic hyperuricemia is independently associated with coronary artery calcification in the absence of overt coronary artery disease: A single-center cross-sectional study. Medicine (Baltimore) 2017;96:e6565.

[84] Jun JE, Lee YB, Lee SE, Ahn JY, Kim G, Jin SM, et al. Elevated serum uric acid predicts the development of moderate coronary artery calcification independent of conventional cardiovascular risk factors. Atherosclerosis 2018;272:233-9.

[85] Song M, Li N, Yao Y, Wang K, Yang J, Cui Q, et al. Longitudinal association between serum uric acid levels and multiterritorial atherosclerosis. J Cell Mol Med 2019;23:4970-9.

[86] Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R. Elevated uric acid increases the risk for kidney disease. J Am Soc Nephrol 2008;19:2407-13.

[87] Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS. Uric acid and incident kidney disease in the community. J Am Soc Nephrol 2008;19:1204-11.

[88] Bellomo G, Venanzi S, Verdura C, Saronio P, Esposito A, Timio M. Association of uric acid with change in kidney function in healthy normotensive individuals. Am J Kidney Dis 2010;56:264-72.

[89] Ben-Dov IZ, Kark JD. Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. Nephrol Dial Transplant 2011;26:2558-66.

[90] Kamei K, Konta T, Hirayama A, Suzuki K, Ichikawa K, Fujimoto S, et al. A slight increase within the normal range of serum uric acid and the decline in renal function: associations in a community-based population. Nephrol Dial Transplant 2014;29:2286-92.

[91] Domrongkitchaiporn S, Sritara P, Kitiyakara C, Stitchantrakul W, Krittaphol V, Lolekha P, et al. Risk factors for development of decreased kidney function in a

southeast Asian population: a 12-year cohort study. J Am Soc Nephrol 2005;16:791-9.

[92] Sedaghat S, Hoorn EJ, van Rooij FJ, Hofman A, Franco OH, Witteman JC, et al. Serum uric acid and chronic kidney disease: the role of hypertension. PLoS One 2013;8:e76827.

[93] Ficociello LH, Rosolowsky ET, Niewczas MA, Maselli NJ, Weinberg JM, Aschengrau A, et al. High-normal serum uric acid increases risk of early progressive renal function loss in type 1 diabetes: results of a 6-year follow-up. Diabetes Care 2010;33:1337-43.

[94] Zoppini G, Targher G, Chonchol M, Ortalda V, Abaterusso C, Pichiri I, et al. Serum uric acid levels and incident chronic kidney disease in patients with type 2 diabetes and preserved kidney function. Diabetes Care 2012;35:99-104.

[95] Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, et al. Relationship of uric acid with progression of kidney disease. Am J Kidney Dis 2007;50:239-47.

[96] Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S. Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. Am J Kidney Dis 2004;44:642-50.

[97] Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. Arch Intern Med 2009;169:342-50.

[98] Haririan A, Metireddy M, Cangro C, Nogueira JM, Rasetto F, Cooper M, et al. Association of serum uric acid with graft survival after kidney transplantation: a time-varying analysis. Am J Transplant 2011;11:1943-50.

[99] Haririan A, Nogueira JM, Zandi-Nejad K, Aiyer R, Hurley H, Cooper M, et al. The independent association between serum uric acid and graft outcomes after kidney transplantation. Transplantation 2010;89:573-9.

[100] Kaufeld T, Foerster KA, Schilling T, Kielstein JT, Kaufeld J, Shrestha M, et al. Preoperative serum uric acid predicts incident acute kidney injury following cardiac surgery. BMC Nephrol 2018;19:161.

[101] Lapsia V, Johnson RJ, Dass B, Shimada M, Kambhampati G, Ejaz NI, et al. Elevated uric acid increases the risk for acute kidney injury. Am J Med 2012;125:302 e9-17.

[102] Viazzi F, Leoncini G, Ratto E, Falqui V, Parodi A, Conti N, et al. Mild hyperuricemia and subclinical renal damage in untreated primary hypertension. Am J Hypertens 2007;20:1276-82.

[103] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29-42.

[104] Burnier M, Roch-Ramel F, Brunner HR. Renal effects of angiotensin II receptor blockade in normotensive subjects. Kidney Int 1996;49:1787-90.

[105] Electronic Medicines Compendium. Allopurinol tablets. Summary of product characteristics, https://www.medicines.org.uk/emc/search?q=allopurinol 2018 [Accessed September 10, 2018].

[106] European Medicines Agency. Adenuric (febuxostat) film-coated tablets. Summary of product characteristics, http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000777/WC500021812.pdf 2018 [Accessed September 10, 2018].

[107] US Food and Drug Administration. ULORIC (febuxostat) tablet for oral use. Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021856s012lbl.pdf 2018 [Accessed September 10, 2018].

[108] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda J, et al. 2018 updated European League Against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis 2020;79:31-8.

[109] Borghi C, Perez-Ruiz F. Urate lowering therapies in the treatment of gout: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2016;20:983-92.

[110] Feig DI, Nakagawa T, Karumanchi SA, Oliver WJ, Kang DH, Finch J, et al. Hypothesis: uric acid, nephron number, and the pathogenesis of essential hypertension. Kidney Int 2004;66:281-7.

[111] Feig DI, Soletsky B, Johnson RJ. Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. JAMA 2008;300:924-32.

[112] Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. Hypertension 2012;60:1148-56.

[113] Beattie CJ, Fulton RL, Higgins P, Padmanabhan S, McCallum L, Walters MR, et al. Allopurinol initiation and change in blood pressure in older adults with hypertension. Hypertension 2014;64:1102-7.

[114] McMullan CJ, Borgi L, Fisher N, Curhan G, Forman J. Effect of uric acid lowering on renin-angiotensin-system activation and ambulatory BP: a randomized controlled trial. Clin J Am Soc Nephrol 2017;12:807-16.

[115] Segal MS, Srinivas TR, Mohandas R, Shuster JJ, Wen X, Whidden E, et al. The effect of the addition of allopurinol on blood pressure control in African Americans treated with a thiazide-like diuretic. J Am Soc Hypertens 2015;9:610-9 e1.

[116] Gunawardhana L, McLean L, Punzi HA, Hunt B, Palmer RN, Whelton A, et al. Effect of febuxostat on ambulatory blood pressure in subjects with hyperuricemia and hypertension: a phase 2 randomized placebo-controlled study. Journal of the American Heart Association 2017;6:e006683.

[117] Kimura K, Hosoya T, Uchida S, Inaba M, Makino H, Maruyama S, et al. Febuxostat therapy for patients with stage 3 CKD and asymptomatic hyperuricemia: a randomized trial. Am J Kidney Dis 2018;72:798-810.

[118] Agarwal V, Hans N, Messerli FH. Effect of allopurinol on blood pressure: a systematic review and meta-analysis. J Clin Hypertens 2013;15:435-42.

[119] Takir M, Kostek O, Ozkok A, Elcioglu OC, Bakan A, Erek A, et al. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. J Investig Med 2015;63:924-9.

[120] Meng J, Li Y, Yuan X, Lu Y. Effects of febuxostat on insulin resistance and expression of high-sensitivity C-reactive protein in patients with primary gout. Rheumatol Int 2017;37:299-303.

[121] Perez-Pozo SE, Schold J, Nakagawa T, Sanchez-Lozada LG, Johnson RJ, Lillo JL. Excessive fructose intake induces the features of metabolic syndrome in healthy adult men: role of uric acid in the hypertensive response. Int J Obes 2010;34:454-61.

[122] Sedhom S, Badary O, Salama S, Mokhles M. Assessment of the therapeutic effect of allopurinol on patients with non-alcoholic fatty liver disease associated with hyperuricemia by cytokeratin 18. J Gastrointest Dig Syst 2016;6:69.

[123] MacIsaac RL, Salatzki J, Higgins P, Walters MR, Padmanabhan S, Dominiczak AF, et al. Allopurinol and cardiovascular outcomes in adults with hypertension. Hypertension 2016;67:535-40.

[124] Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation 2002;105:2619-24.

[125] Farquharson CA, Butler R, Hill A, Belch JJ, Struthers AD. Allopurinol improves endothelial dysfunction in chronic heart failure. Circulation 2002;106:221-6.

[126] Rajendra NS, Ireland S, George J, Belch JJ, Lang CC, Struthers AD. Mechanistic insights into the therapeutic use of high-dose allopurinol in angina pectoris. J Am Coll Cardiol 2011;58:820-8.

[127] Higgins P, Dawson J, Lees KR, McArthur K, Quinn TJ, Walters MR. Xanthine oxidase inhibition for the treatment of cardiovascular disease: a systematic review and meta-analysis. Cardiovasc Ther 2012;30:217-26.

[128] Singh JA, Yu S. Allopurinol reduces the risk of myocardial infarction (MI) in the elderly: a study of Medicare claims. Arthritis Res Ther 2016;18:209.

[129] Singh JA, Yu S. Allopurinol and the risk of stroke in older adults receiving Medicare. BMC Neurol 2016;16:164.

[130] Ogino K, Kato M, Furuse Y, Kinugasa Y, Ishida K, Osaki S, et al. Uric acid-lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. Circ Heart Fail 2010;3:73-81.

[131] Kojima S, Matsui K, Hiramitsu S, Hisatome I, Waki M, Uchiyama K, et al. Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDy. Eur Heart J 2019;40:1778-86.

[132] Zhang M, Solomon DH, Desai RJ, Kang EH, Liu J, Neogi T, et al. Assessment of cardiovascular risk in older patients with gout initiating febuxostat versus allopurinol. Circulation 2018;138:1116-26.

[133] Yokota T, Fukushima A, Kinugawa S, Okumura T, Murohara T, Tsutsui H. Randomized trial of effect of urate-lowering agent febuxostat in chronic heart failure patients with hyperuricemia (LEAF-CHF). Int Heart J 2018;59:976-82.

[134] Kanbay M, Huddam B, Azak A, Solak Y, Kadioglu GK, Kirbas I, et al. A randomized study of allopurinol on endothelial function and estimated glomular filtration rate in asymptomatic hyperuricemic subjects with normal renal function. Clin J Am Soc Nephrol 2011;6:1887-94.

[135] Tani S, Nagao K, Hirayama A. Effect of febuxostat, a xanthine oxidase inhibitor, on cardiovascular risk in hyperuricemic patients with hypertension: a prospective, open-label, pilot study. Clin Drug Investig 2015;35:823-31.

[136] Levy GD, Rashid N, Niu F, Cheetham TC. Effect of urate-lowering therapies on renal disease progression in patients with hyperuricemia. J Rheumatol 2014;41:955-62.

[137] Singh JA, Yu S. Are allopurinol dose and duration of use nephroprotective in the elderly? A Medicare claims study of allopurinol use and incident renal failure. Ann Rheum Dis 2017;76:133-9.

[138] Goicoechea M, de Vinuesa SG, Verdalles U, Ruiz-Caro C, Ampuero J, Rincon A, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010;5:1388-93.

[139] Sircar D, Chatterjee S, Waikhom R, Golay V, Raychaudhury A, Pandey R. Efficacy of febuxostat for slowing the GFR decline in patients with ckd and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. Am J Kidney Dis 2015;66:945-50.

[140] Lin TC, Hung LY, Chen YC, Lo WC, Lin CH, Tam KW, et al. Effects of febuxostat on renal function in patients with chronic kidney disease: A systematic review and meta-analysis. Medicine (Baltimore) 2019;98:e16311.

[141] Sato Y, Feig DI, Stack AG, Kang DH, Lanaspa MA, Ejaz AA, et al. The case for uric acid-lowering treatment in patients with hyperuricaemia and CKD. Nat Rev Nephrol 2019;15:767-75.

Tables

Table 1

Estimates of the prevalence of hyperuricaemia around the world.

Survey	Date published	Population studied	Geographical area	Date or period of assessment	Threshold	Prevalence
NHANES-III [6]	2011	Representative sample of the adult non-institutionalised civilian population	USA	1988–1994	Men: >7.0 mg/dL Women: >5.7 mg/dL	19.1%
NHANES [6]	2011	Representative sample of the adult non-institutionalised civilian population	USA	2007–2008	Men: >7.0 mg/dL Women: >5.7 mg/dL	21.5%
NHANES [4]	2012	Representative sample of the adult non-institutionalised civilian population	USA	2009–2010	Men: acid >7.0 mg/dL Women: >6 mg/dL	19.3%
Miao et al. 2008 [9]	2008	Random sample of individuals aged 20–80 years who have lived in the same place for >5 years	Coastal cities of Eastern China	2004	Men and postmenopausal women: >7.0 mg/dL	13.2%

					Premenopausal women: >6 mg/dL	
NAHSIT [7]	2011	Adults	Taiwan	1993–1996	Men: >7.7 mg/dL	25.3%
					Women: >6.6 mg/dL	16.7%
NAHSIT [7]	2011	Adults	Taiwan	2005–2008	Men: >7.7 mg/dL	22.0%
					Women: >6.6 mg/dL	9.7%
Trifiro et al. 2013 [8]	2013	Representative sample of the adult general population	Italy	2005	>6 mg/dL	85.4[a]
Trifiro et al. 2013 [8]	2013	Representative sample of the adult general population	Italy	2009	>6 mg/dL	119.3[a]

[a]Cases per 1000 inhabitants.

NAHSIT: Nutrition and Health Survey in Taiwan; NHANES: National Health and Nutrition Examination Survey.

Table 2

Meta-analyses of studies investigating the association of hyperuricaemia on selected clinical outcomes.

Publication	Date published	Search criteria	Number of primary studies (number of participants)	Major findings
Hypertension				
Grayson et al. [40]	2011	Databases: MEDLINE, EMBASE, Cochrane Library Publication dates: 1980 to April 2010 Design: prospective cohort studies, >1 year follow-up Participants: patients had no hypertension at the onset, sample size ≥100 patients Exposure: SUA Outcome: incidence of hypertension	18 (55,607)	• For every 1 mg/dL increase in SUA, the risk of hypertension increased by 13% • The effect is significantly larger in younger patients (p = 0.02) • Hyperuricaemia is associated with a significant risk of hypertension
Wang et al. [41]	2014	Databases: MEDLINE, EMBASE, CBM Publication dates: through September 2013	25 (97,824)	• For every 1 mg/dL increase in SUA, the risk of hypertension increased by 15%

		Design: prospective and retrospective cohort and nested case-control studies, >1 year follow-up Participants: patients had no hypertension at the onset, sample size ≥100 patients Exposure: SUA Outcome: incidence of hypertension		• Hyperuricaemia is associated with a modest increase in the risk of hypertension
Uric acid-lowering therapy				
Agarwal et al. [118]	2013	Databases: Medline, PubMed, EMBASE, Cochrane Library Publication dates: 1966 to February 2012 Design: prospective and retrospective, parallel or cross-over studies, duration ≥4weeks for each arm Participants: humans Exposure: allopurinol Outcome: BP	10 (738)	• In patients treated with allopurinol, SBP decreased by 3.3 mmHg (p = 0.001) and DBP decreased by 1.3 mmHg (p = 0.03) compared with controls • When only randomised controlled studies were considered, these values were 3.3 mmHg (p < 0.001) and 1.4 mmHg (p = 0.04), respectively • Allopurinol is associated with a small but significant reduction in BP
Pre-eclampsia				

Thangaratinam et al. [43]	2006	Databases: MEDLINE (1951–2004), EMBASE (1980–2004), Cochrane Library (2004:4), MEDION (a database of diagnostic test reviews set up by Dutch and Belgian researchers) Exposure: SUA Outcome: maternal or foetal complications	18 (3,913)	• In women with pre-eclampsia, SUA is a poor predictor of both maternal and foetal complications
Cardiovascular diseases				
Wheeler et al. [63]	2005	Databases: MEDLINE, PubMed, Web of Science, EMBASE Publication dates: before May 2003 Design: prospective studies, >1 year follow-up Exposure: SUA Outcome: incidence of CHD	16 (9,458 CHD cases, 155,084 controls)	• In individuals at the top third of the SUA distribution, the odds ratio for CHD was 1.12 after adjusting for age, sex and risk factors • In the 8 studies that employed a more extensive adjustment for possible confounders, the odds ratio was 1.02 • SUA is a poor predictor of CHD in the general population
Huang et al. [72]	2014	Databases: EMBASE (1974 to May 2013), MEDLINE (1946 to May 2013), CBM (1978 to May 2013) Exposure: SUA	5 studies on incident HF 28 studies on outcomes in patients with HF	• For every 1 mg/dL increase in SUA, the risk of HF increased by 19%, of all-cause mortality by 4% and of the composite of death and cardiac events by 28%

		Outcome: incidence of HF, outcomes in patients with HF		• Elevated SUA is associated with an increased risk of HF and poor outcomes
Li et al. [71]	2014	Databases: PubMed, EMBASE, Cochrane Library Publication dates: before July 2013 Design: community- or population-based studies, >1 year follow-up Participants: adult patients free of kidney disease at baseline Exposure: SUA Outcome: risk ratio for stroke and death	15 (1,042,358)	• In patients with hyperuricaemia, the relative risk of stroke was 1.22 and the relative risk of death was 1.33 • Hyperuricaemia is associated with a modestly increased risk of stroke and death from stroke
Metabolic diseases				
Kodama et al. [58]	2009	Databases: MEDLINE (1966 to 2009), EMBASE (1980 to 2009) Design: observational cohort studies Exposure: SUA Outcome: risk of T2D	11 (42,834)	• For every 1 mg/dL increase in SUA, the risk of T2D increased by 17% • Significant publication bias was observed (p = 0.03) • The estimate of the risk of T2D was reduced after adjustment for publication bias to 11% for every 1 mg/dL (p = 0.009)

Lv et al. [60]	2013	Databases: PubMed Publication dates: before April 2012 Design: prospective cohort studies Exposure: SUA Outcome: incidence of T2D	8 (32,016)	• For every 1 mg/dL increase in SUA, the risk of T2D increased by 6% • The association between SUA and T2D was consistent across subgroup analyses, including components of metabolic syndrome
Liu et al. [54]	2015	Databases: PubMed, EMBASE, ISI database Publication dates: before May 2015 Design: prospective cohort studies Participants: adults free of metabolic syndrome at baseline Exposure: SUA Outcome: risk of metabolic syndrome	7 (23,081 men, 12,195 women)	• For every 1 mg/dL increase in SUA, the risk of metabolic syndrome increased by 5% in males and 9% in females • The risk of metabolic syndrome was higher in younger women (17%, $p < 0.05$)

BP: blood pressure; CBM: Chinese Biomedicine Database; CHD: coronary heart disease; DBP: diastolic blood pressure; HF: heart failure; ISI: Institute for Scientific Information; SBP: systolic blood pressure; SUA: serum uric acid.

Figure legend

Fig. 1. Hyperuricaemia as a predictive factor for the development of various disease states.