Review

Uric acid and hypertension: a focused review and practical recommendations

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Uric acid levels are higher in humans than in other mammals. Best known as an extracellular antioxidant, uric acid also increases salt sensitivity, fat storage, and lipogenesis. Xanthine oxidase-related oxidative stress may also induce endothelial dysfunction and renal vasoconstriction. Renal structure abnormalities contribute to salt-sensitive and uric acid-independent hypertension. Maternal hyperuricemia during pregnancy and hyperuricemia early in life are likewise independent risk factors for hypertension. Genetic polymorphism is potentially involved in the activity of xanthine oxidoreductase, but further studies are needed. Xanthine oxidase inhibition consistently decreases blood pressure in younger hypertensive patients, albeit modestly. Hyperuricemia affects one out of five adults as a result of the Western diet, insulin resistance, and renal dysfunction. This review advocates lifestyle changes to maintain uric acid levels within the normal range in young (pre)hypertensive individuals or normotensives with a family history of hypertension, metabolic disorders, or obesity; moreover, antihypertensive medications that increase uric acid levels should be avoided.

Keywords: hypertension, hyperuricemia, oxidative stress, xanthine oxidoreductase

Abbreviations: CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; GLUT9, glucose transporter type 9; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; RAS, renin–angiotensin system; ROS, reactive oxygen species; URAT1, urat transporter 1; XDH, xanthine dehydrogenase; XOR, xanthine oxidoreductase

INTRODUCTION

The link between hypertension and uric acid was first hypothesized by Mahomed *et al.* in the 1870s [1]. In 1966, Cannon *et al.* [2] showed that 47% of hypertensive patients were also hyperuricemic. Since then, many epidemiological studies have demonstrated a strong association between uric acid and hypertension [3]. A recent systematic review and meta-analysis revealed that a 1.0 mg/dl (60 μmol/l) increase in uric acid level is associated with an increased risk of incident hypertension by 13% [95% confidence interval (CI) 1.06–1.20]. The effect of uric acid on hypertension is more pronounced in younger populations and in women [4]. Therefore, although the evidence is based primarily on cross-sectional studies, uric acid is considered an independent risk factor, nay a causative factor for hypertension by some experts, especially earlier in life [5,6]. Others showed that this association was stronger among men than women, possibly because of the uricosuric effect of oestrogens [7]. Asymptomatic hyperuricemia was also reported to be a strong risk factor for refractory hypertension in the elderly [8]. These results contrast with Mendelian randomization studies that have examined genetic polymorphisms involved in the renal handling of uric acid and that suggest these genes most likely do not directly increase the risk of cardiovascular disease [9]. More recent studies have investigated the relevance of genetic polymorphisms affecting xanthine oxidoreductase (XOR)-activity, with disparate conclusions [10,11].

Maternal hyperuricemia during pregnancy is associated with an increased risk of hypertension in the offspring [1]. Eclampsia-induced endothelial dysfunction leads to a decreased number of nephrons, which subsequently increases the risk of hyperuricemia, arteriolopathy and salt-sensitive hypertension in children.

Associations between uric acid and cardiovascular disease and mortality, coronary heart disease, cerebrovascular accident, congestive heart failure [12], heart failure with preserved ejection fraction (in hypertensive patients) [13], metabolic syndrome [14], subclinical atherosclerosis [5], kidney disease, and endothelial dysfunction [14] have also been reported. However, in all these clinical circumstances, the question of causality remains questionable.

Nevertheless, these data suggest that high uric acid levels contribute to the pathogenesis of cardiovascular disease. However, in adults, there is still no convincing evidence that lowering uric acid levels improves blood pressure control or prevents hypertension or cardiovascular disease.

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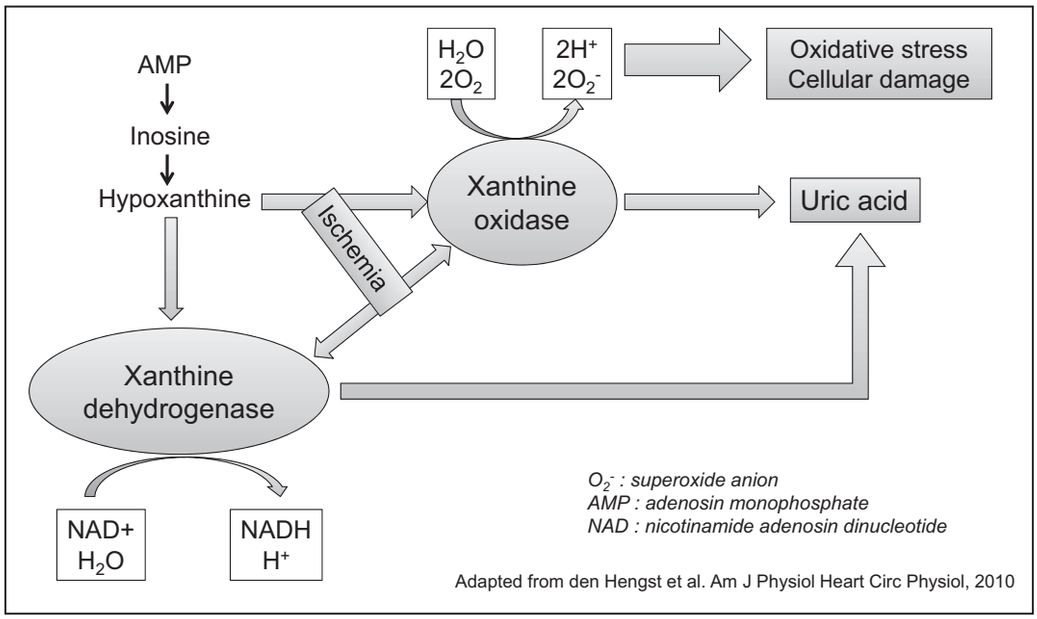

FIGURE 1 Xanthine oxidoreductase exists in two interconvertible isoforms in the liver, intestine and vascular wall. Xanthine dehydrogenase is predominant and uses nicotinamide adenine dinucleotide (NAD+) as electron acceptor and does not produce reactive oxygen species. Xanthine oxidase is the main form in ischemic conditions, after extensive surgery or physiologic stress. Xanthine oxidase preferentially uses oxygen as electron acceptor and thus, is able to produce reactive oxygen species with oxidative stress and cellular damage as consequences.

Thus, the potential benefit of uric acid-lowering strategies in the later stages of developing hypertension remains unknown.

With the advent of improved therapies for hyperuricemia, the purpose of this focused review is to present the recent evidence on how uric acid may relate to hypertension, what level of uric acid is preferable in prehypertensive and hypertensive patients, and how such targets can be achieved.

METHODS

A comprehensive search was performed on PubMed. We used MeSH terms as well as free text words for key words. Key words were 'uric acid' or 'urate' or 'hyperuricemia' and 'hypertension' or 'blood pressure' for the main topic. Articles cited by the authors of the articles from the initial search were also reviewed. Then, we used the following key words for animal and in-vitro studies: 'mice' or 'mouse' or 'rat' or 'rodent' and 'uric acid' or 'urate' or 'hyperuricemia,' 'endothelial cell,' 'smooth muscle cell' or 'human umbilical vein endothelial cell,' 'endothelial function,' 'endothelium' and 'oxidative stress.' To find articles discussing treatment effects, we used the key words 'allopurinol,' 'febuxostat,' 'probenecid,' 'urate oxidase,' 'rasburicase' together with previous key words. Only articles written in English and published in international peer reviewed journals were analyzed.

Metabolism

Uric acid is the final product of purine metabolism. The main enzyme involved in the pathway is XOR, which exists in two interconvertible isoforms: xanthine dehydrogenase (XDH) and xanthine oxidase. Only xanthine oxidase creates reactive oxygen species (ROS) (see Fig. 1). This latter isoform is more active in ischemic conditions, after extensive surgery or physiologic stress, and is mainly expressed by the liver, intestine and vascular wall. Uric acid is primarily excreted by the kidney (85%) as a poorly soluble substance in urine and by the small bowel. In the kidney, uric acid is almost entirely reabsorbed by different transporters [mainly urate transporter 1 (URAT1)] in the proximal tubule with a excretion rate of 10% [15]. In the small bowel, the excretion pathway involves the glucose transporter type 9 (GLUT9).

In most mammals, uricase (urate oxidase) catalyzes uric acid into allantoin, a soluble metabolite easier to eliminate. During the Miocene Era, great apes lost uricase activity [16]. Hence, large primates tend to have higher uric acid levels compared with other mammals. The loss of uricase function and high reabsorption rate of uric acid supposedly provided some evolutionary advantages. First, uric acid acts as an antioxidant and represents more than 60% of the antioxidant capacity of plasma. It scavenges oxidant radicals, reacts with peroxynitrite, and stabilizes endothelial nitric oxide synthase (eNOS) activity. Its effects require the presence of ascorbate [16]. Importantly, extremely low uric acid levels are associated with endothelial dysfunction [17] and there is a J-shaped relationship between cardiovascular events and uric acid levels in primary hypertensive men and women [18]. Second, uric acid increases salt sensitivity and may maintain blood pressure in a salt-poor environment, which might have been beneficial historically when salt intake was supposedly very low [16]. Third, uric acid increases fat storage and triglycerides. As fruits contain more fructose at the end of summer, enhancement of lipid deposition may have allowed early man to better cope with the oncoming winters [16].

TABLE 1. Causes of hyperuricemia

Alcohol consumption
High intake of fructose, seafood, fatty meats
Loop and thiazide diuretics
Genetic polymorphisms in URAT1 and GLUT9
Insulin resistance
Obesity
Chronic kidney disease
Small bowel disease
High cell turn-over and protein degradation

GLUT9, glucose transporter type 9; URAT1, urate transporter 1.

Causes of hyperuricemia

Normal serum uric acid levels are between 3.0 and 6.5 mg/dl (180 and 385 μmol/l). In the United States of America, approximately one out of five adults have hyperuricemia (uric acid levels >7.0 mg/dl, >415 μmol/l for men; >5.7 mg/dl, >340 μmol/l for women) [19]. Reduced uric acid excretion (renal failure or hyperinsulinemia) is a common cause of hyperuricemia. High cell turnover and the Western diet are also a large source of purines. Fatty or red meats, seafood, alcohol and sugar-sweetened (especially fructose) beverages are well known to increase uric acid levels. Loop and thiazide diuretics induce a relative hypovolemia, which leads to a compensatory increase in proximal uric acid reabsorption. This mechanism reduces renal uric acid excretion. Genetic polymorphisms in URAT1 and GLUT9 can also result in hyperuricemia [20] (see Table 1).

Fructose is the only sugar, which can raise uric acid levels. Its first metabolizing step consumes a large amount of adenosine triphosphate, resulting in substrates for purine metabolism [21]. Some animal and human studies have shown that a large quantity of fructose leads to hyperuricemia and elevated blood pressure [20,22].

Animal models and in-vitro studies

Although the application of results from animal models is sometimes challenging, these studies provide important information about the pathogenic role of uric acid in hypertension. Uricase-knockout rodents die within a few weeks of renal tubular crystal deposition and renal failure. Mild-to-moderate experimentally induced hyperuricemia (by administration of oxonic acid) is associated with increased blood pressure after several weeks, without evidence of crystal deposition in the kidney. This model suggests that hypertension develops in two steps (see Fig. 2). First, uric acid activates the renal renin–angiotensin system (RAS), reduces NO bioavailability (decreased NOS expression) and increases oxidative stress in the macula densa, leading to endothelial dysfunction and renal vasoconstriction. This first step is in part uric acid-dependent and occurs without any identifiable renal structure

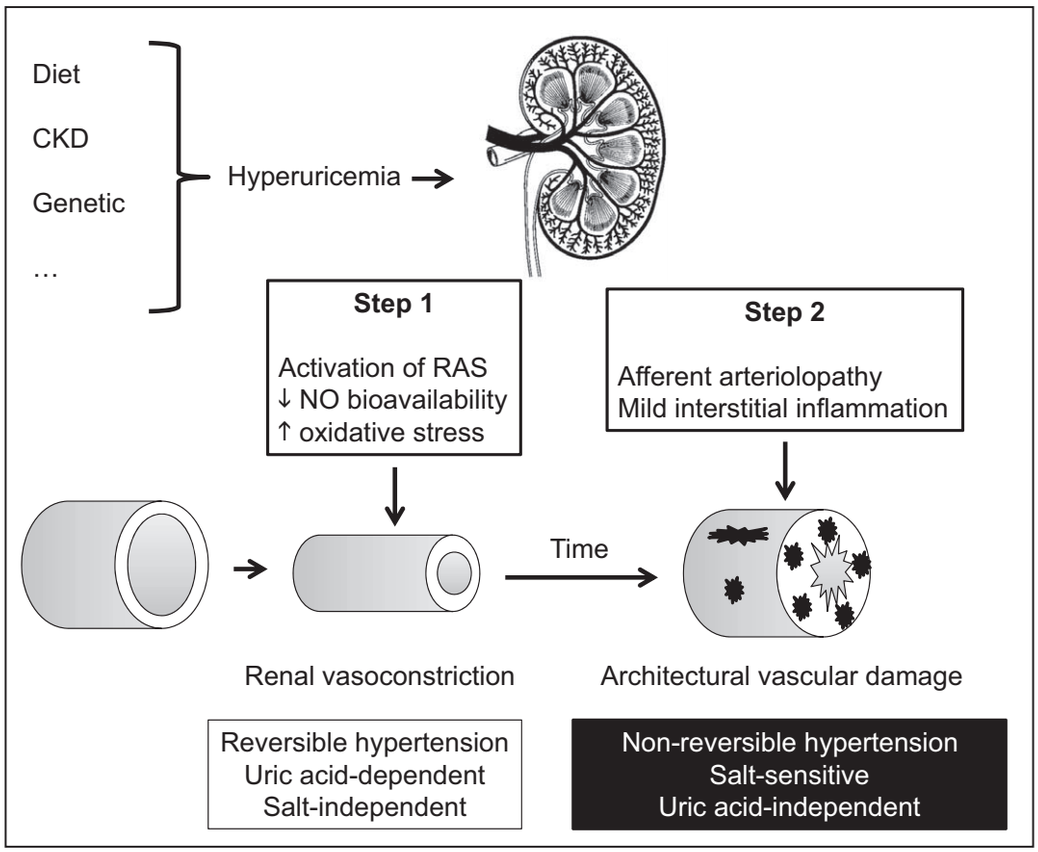

FIGURE 2 Animal models suggest uric acid acts in two steps to induce hypertension. First, uric acid raises secretion of renin, reduces nitric oxide bioavailability and increases oxidative stress. This first step leads to renal vasoconstriction and a reversible uric acid-dependent and salt-independent hypertension. After several weeks of persistent elevated uric acid levels, architectural vascular damage occurs with afferent arteriolopathy and mild interstitial inflammation. At this second stage, hypertension becomes salt-sensitive and does not respond to uric acid-lowering therapies. CKD, chronic kidney disease; NO, nitric oxide; RAS, renin–angiotensin system.

abnormality. Second, after several weeks, architectural vascular damage such as afferent arteriolopathy and mild interstitial inflammation develops, resulting in a salt-sensitive and uric acid-independent hypertensive state [20]. These latter changes are similar to those observed in most patients with primary hypertension [23]. The above mentioned first step could be potentially reversible before renal damage occurs by administration of xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric agents (benzbromarone and probenecid), L-arginine supplementation (a substrate for NOS), or RAS blockers [20,24].

Another animal model of hyperuricemia has been developed via hepatocyte-specific deletion of GLUT9, a transporter protein that provides uric acid substrate for the hepatocellular enzyme uricase [25]. A three-fold to four-fold increase in uricemia (induced gradually by addition of inosine to the diet) failed to affect 24 h blood pressure until the animals developed renal lesions. This suggests that the effect of uric acid on blood pressure is secondary to renal damage, which hyperuricemia may mediate.

In endothelial cells, uric acid blocks NO release [26]. It also stimulates synthesis of pro-inflammatory factors such as C-reactive protein (CRP), angiotensin-II, interleukin-6, interleukin-8, tumour necrosis factor alpha, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and monocyte chemoattractant protein-1 (MCP-1) [27]. These effects are attributed to ROS production and lead to apoptosis and inhibition of cell proliferation and migration [28]. In vascular smooth muscle cells, uric acid stimulates cell proliferation and migration via production of CRP, cyclooxygenase-2, MCP-1, local thromboxane, angiotensin-II, and upregulation of platelet-derived growth factor-A [20].

Human clinical trials

Hyperuricemia (>5.5 mg/dl, >330 μmol/l) is seen in up to 89% of newly primary hypertensive paediatric patients. In a small placebo-controlled crossover study of 30 morbidly obese adolescents, allopurinol normalized blood pressure in 66% of patients after 4 weeks [29]. In another randomized trial, 60 obese children received allopurinol, probenecid, or placebo for 7 weeks. Uric acid-lowering therapies significantly decreased office and 24-h ambulatory blood pressure by 10 mmHg [30]. In an open-label randomized study, allopurinol also enhanced the antihypertensive effects of enalapril in hyperuricemic primary hypertensive children, among which 37% were obese [31].

In adults, clinical trial results are less convincing because of the limited number of well conducted, randomized, prospective studies. In one nonrandomized study, allopurinol (300 mg/day for 3 months) reduced blood pressure and CRP levels in asymptomatic hyperuricemic adults [32]. A systematic review and meta-analysis reported that allopurinol had a minimal clinical effect in reducing SBP by 3.3 mmHg and DBP by 1.3 mmHg [33]. A phase II, randomized, placebo-controlled study recently showed that febuxostat decreased SBP in a preplanned subgroup analysis of hyperuricemic hypertensive patients with normal renal function [34]. Other studies on elderly patients did not show any effects of lowering uric acid levels on blood pressure, consistent with the lack of correlation between serum uric acid and hypertension in this population [35,36]. In overweight and obese adults with uric acid levels greater than 5.0 mg/dl (>300 μmol/l), neither allopurinol nor probenecid improved blood pressure or affected RAS activity [37]. Results of the LIFE study suggested that losartan reduces the incidence of cardiovascular events better than atenolol because of its uricosuric effects [38].

According to a recent meta-analysis, there remains a lack of quality evidence to recommend the use of uric acid-lowering therapies to improve blood pressure control in hypertensive adults [39]. In heart failure patients with or without hyperuricemia, allopurinol improved endothelial function compared with placebo and probenecid, but more data are needed [40]. Similarly, allopurinol improved endothelial function in type 2 diabetic patients with mild hypertension and smokers [41]. There was no effect on endothelial function in healthy controls.

DISCUSSION

Heterogeneous results from studies of the relationship between uric acid and endothelial function, hypertension and cardiovascular disease generate several perplexing questions, foremost among which whether uric acid per se or ROS production by xanthine oxidase is responsible for the above-mentioned deleterious effects. An argument against a causal relationship between uric acid and hypertension is that uric acid infusion does not alter endothelial function in healthy subjects [42]. Evidence to the contrary is that uric acid infusion improved endothelial function of coronary arteries in isolated perfused hearts [43], as well as in type 1 diabetics and smokers [44]. Furthermore, lowering uric acid in type 2 diabetics with intravenous recombinant uricase did not improve endothelial function [45]. A recent study failed to show any effect of large increase or decrease in uric acid level on blood pressure (through uric acid or uricase infusion, respectively) [46]. Thus, experimentally induced changes in extracellular uric acid levels do not appear to directly influence endothelial dysfunction. Extremely low uric acid levels seen in the setting of URAT1 mutation are associated with endothelial dysfunction [17] and low uric acid levels appear to be linked to an increased risk of cardiovascular events [18].

A growing hypothesis is that uric acid acts as an antioxidant factor in the extracellular space, but as a pro-oxidant factor inside the cell [6]. This may explain why acute uric acid infusion improved extracellular antioxidant properties in some [43,44], but not all studies [42]. If this hypothesis is correct, long-term effects of uric acid infusion may be deleterious once intracellular uric acid levels are increased. Reduction of uric acid with uricase did not affect endothelial function in diabetics [45]. This finding may be explained by the oxidation of uric acid into allantoin by uricase, thereby increasing production of ROS and/or loss of antioxidant effects of uric acid through depletion. Conversely, xanthine oxidase inhibitors such as allopurinol improved endothelial function by reducing uric acid levels and ROS production within the cells [41], an effect not seen with probenecid [6,40].

Another proposed hypothesis suggests that hyperuricemia resulting from a high rate of production is more harmful than hyperuricemia caused by reduced excretion (kidney disease) or increased reabsorption (diuretics) [47]. The rationale is that increased formation of uric acid by xanthine oxidase generates high levels of ROS [48] that cause cardiovascular, metabolic, and renal diseases through the cellular effects of oxidative stress. Thus, xanthine oxidase inhibitors would seem to be more efficacious than uricosuric agents by reducing uric acid levels and ROS production. Although more trials are needed to determine the appropriate role of xanthine oxidase inhibitors in control of cardiovascular risk factors, we suggest selecting patients according to their cardiovascular risk and not only by their uric acid levels (as most past studies have). Indeed, cardiovascular disease and gout are likely two completely different diseases – unless their pathogenesis is linked by xanthine oxidase hyperactivity and increased ROS production.

In conclusion, according to the available data, uric acid is associated with cardiovascular, renal and metabolic diseases. Among these disease states, the link between uric acid levels and hypertension seems to be the strongest, given sound experimental evidence of its pathophysiologic basis. Therefore, in children, adolescents and young adults with a family history of prehypertension (120–139/80–89 mmHg) or hypertension (>140/90 mmHg), especially if other comorbidities (obesity, diabetes) are present, we recommend monitoring and maintaining uric acid levels below the upper limit of normal [5.5, 6.0 and 7.0 mg/dl (330, 360, and 415 μmol/l) for children, women and men, respectively]. Specific diets and uricosuric antihypertensive drugs (losartan) can be used as first choice therapy in these patients; diuretics should be avoided. Currently, we lack evidence from large and well designed clinical trials to justify the use of xanthine oxidase inhibitors for treatment of hypertension, particularly because of their potential side effects. However, febuxostat, which is more specific and better tolerated than allopurinol, may become a drug of choice in this context. Large interventional studies are needed to determine whether reduction in uric acid levels can prevent hypertension and major cardiovascular events – especially in young patients with prehypertension.

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Conflicts of interest

B.D.B. declares no conflicts of interest. P.v.d.B.'s employer received honoraria for lecturing/advisory boards from Amgen, Bayer, Boehgingher-Ingelheim, Daïchi-Sankyo, Idorsia, Menarini, Novo Nordisk, Sanofi. C.B.'s employer received honoraria for lecturing/advisory from Menarini Corporate, Servier, Novartis, Sanofi, Alfasigma, Teijn, Takeda, Astrellas. M.B.'s employer received honoraria for lecturing/advisory from Menarini, Daiichi Sankyo, Amgen and Servier.

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