


Hyperuricemia and Hypertension: Links and Risks

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Abstract: Hyperuricemia has long been recognized to be associated with increased cardiovascular risk, including risk of developing hypertension. Epidemiological findings suggest that the link with hypertension is stronger in children and adolescents. Uric acid acts as a strong antioxidant compound in the extracellular environment but has pro-inflammatory effects within the intracellular setting. A chronic phase of microvascular injury is known to occur after prolonged periods of hyperuricemia. This is proposed to contribute to afferent arteriopathy and elevation of blood pressure that may become unresponsive to uric acid-lowering therapies over time. Studies have struggled to infer direct causality of hyperuricemia due to a vast number of confounders including body mass index. The aim of this review is to present the available data and highlight the need for large scale prospective randomized controlled trials in this area. At present, there is limited evidence to support a role for uric acid-lowering therapies in helping mitigate the risk of hypertension.

Keywords: hyperuricemia, hypertension, urate, cardiovascular, chronic kidney disease

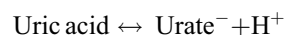
Introduction

Hypertension affects an estimated 1.13 billion people worldwide and the World Health Organization reports that it is implicated in 13% of deaths globally.¹ They have set a target of reducing its prevalence by 25% by the year 2025 (from the 2010 baseline). The etiology of essential hypertension is multifactorial and complex, with an increasing number of contributory factors being appreciated in recent decades. The relationship between uric acid (UA) and blood pressure (BP) is certainly not new and has been recognized for over a century.² Multiple studies have demonstrated an independent association between hyperuricemia and hypertension, although the issue of direct causality is still hotly debated.

The aim of this review is to present the available evidence on the links between hyperuricemia and hypertension with an emphasis on the potential role of UA-lowering therapies in helping mitigate this risk.

Uric Acid Homeostasis

Uric acid ($C_5H_4N_4O_3$), or 2,6,8-trihydroxypurine, is a heterocyclic carbon-based compound with a molecular weight of 168 Da. It is a weak acid with $pK_a \approx 5.8$ in the blood and ≈ 5.35 in the urine. It exists predominantly in its monovalent deprotonated ionic form, the urate anion, within the physiological arterial blood pH of 7.40. As such, the following equation is shifted far to the right:



UA is the end-product of purine mononucleotide catabolism. Purines can be synthesized endogenously or can be derived from dietary sources. Purines perform

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many vital functions within the body. Notably, adenosine triphosphate (ATP) provides the energy to drive intracellular reactions, and the purine nucleobases, adenine and guanine, are integral components of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). The catabolism

of the purine mononucleotides adenylic acid (AMP), guanylic acid (GMP) and inosinic acid (IMP) to UA involves several enzymatic steps (Figure 1). An intermediate step is the production of the purine bases guanine and hypoxanthine. These are then converted to xanthine and

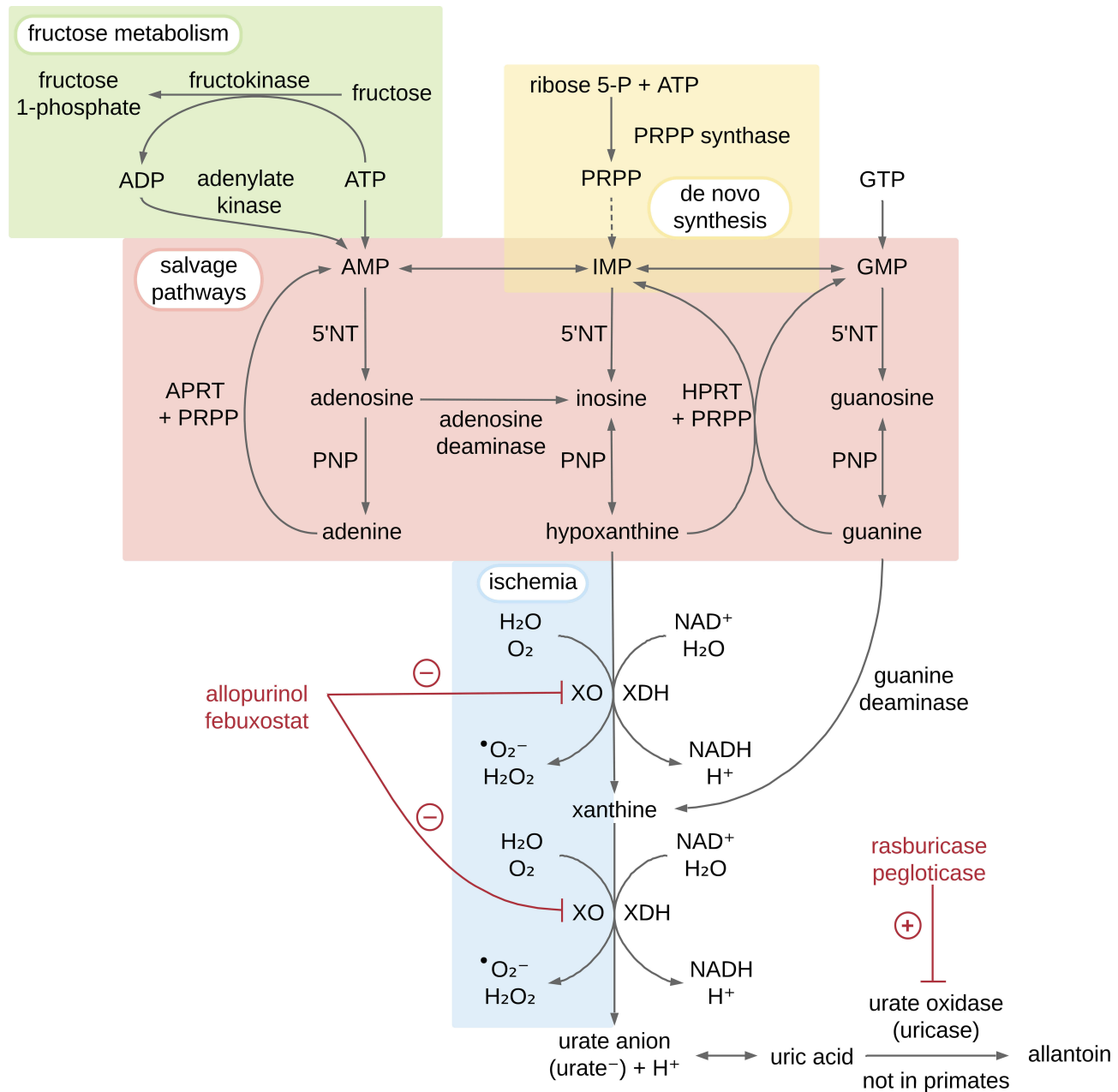


Figure 1 Urate production pathways. De novo synthesis of urate starts with the generation of phosphoribosyl pyrophosphate (PRPP) from ribose 5-phosphate (ribose 5-P) and adenosine triphosphate (ATP), leading to the formation of the purine mononucleotide inosine monophosphate (IMP). IMP is indirectly converted to hypoxanthine, a purine base. Adenosine monophosphate (AMP) and guanosine monophosphate (GMP) are involved in the production of the other purine bases adenine and guanine respectively. Enzymatic salvage pathways exist that allow for further generation of AMP, IMP and GMP from these purine bases. The conversion of fructose to fructose 1-phosphate by fructokinase generates AMP. Under conditions of ischemia, the conversion of hypoxanthine to xanthine, and subsequently to the urate anion, generates superoxide ($\cdot\text{O}_2^-$) and thus stimulates the release of ROS. Allopurinol and febuxostat act as xanthine oxidase (XO) inhibitors to block the formation of urate. Rasburicase and pegloticase are recombinant versions of uricase that promote the breakdown of uric acid (UA) into allantoin.

Abbreviations: ADP, adenosine diphosphate; GTP, guanosine triphosphate; 5'NT, 5'nucleotidase; APRT, adenine phosphoribosyl transferase; HPRT, hypoxanthine-guanine phosphoribosyl transferase; PNP, purine nucleotide phosphorylase; XDH, xanthine dehydrogenase; NAD^+ , nicotinamide adenine dinucleotide (oxidized form); NADP , nicotinamide adenine dinucleotide (reduced form).

irreversibly oxidized to UA by the two interconvertible isoforms of xanthine oxidoreductase (XOR) - xanthine dehydrogenase (XDH) and xanthine oxidase (XO). The latter isoform produces reactive oxygen species (ROS) and is generated under conditions of physiological stress and ischemia. A salvage pathway exists that allows for purine reutilization involving the enzyme hypoxanthine-guanine phosphoribosyltransferase (HPRT).

UA homeostasis is governed by the balance between the rate of UA generation (determined by purine catabolism), renal excretion, and intestinal secretion. UA is derived mainly from the breakdown of purines in the liver and bowel, as well as the kidneys, muscle and vascular endothelium. The exogenous supply of UA is derived from dietary sources of purines including meat, seafood and alcohol. Purine-free formula diets have been associated with approximately a 40% reduction in urinary UA excretion suggesting that diet provides a significant source of urate precursors, despite there being few dietary sources of UA alone.³

UA metabolism in the tissues is minimal and most elimination occurs via the kidneys and intestine. Intestinal excretion of UA is followed by metabolism by gut bacteria in a process called intestinal uricolysis. This accounts for 25–35% of UA elimination, and renal excretion accounts for the remaining 65–75%.⁴ The majority of circulating urate is free with less than 5% albumin-bound. Most urate is therefore readily filtered by the glomeruli, although up to 90% may then be reabsorbed.⁵

Multiple urate transporters have been identified that play a role in renal tubular reabsorption and secretion of urate, thus helping regulate homeostasis (Figure 2) and maintain plasma levels within a range.⁶ The main transporters identified to date are:

- URAT1 (urate transporter 1) – which belongs to the organic acid transporter (OAT) family and is encoded by the *SLC22A12* (solute carrier family 22 member 12) gene on chromosome 11. It was the first urate transporter described in detail and plays a role in urate reabsorption at the apical surface of the proximal tubular epithelium.⁷ It reabsorbs UA in exchange for monovalent anions such as acetoacetate, hydroxybutyrate, lactate and nicotinate. Certain drugs including benzbromarone, probenecid and losartan, are known to exert a uricosuric effect via inhibition of URAT1.⁸
- GLUT9 (glucose transporter 9) – another major urate reabsorptive transporter. This is a hexose transporter

and is encoded by the *SLC2A9* gene on chromosome 4. GLUT9 reabsorbs urate at the basolateral membrane of the proximal tubule and has been demonstrated to be the single most important genetic determinant of serum UA (SUA) levels and hyperuricemia in a large human genome-wide study of 28,141 individuals.^{9,10}

- ABCG2 (ATP-binding cassette subfamily G member 2; encoded by the *ABCG2* gene) – is known to have effects on both intestinal and renal excretion of urate. It acts at the apical surface of the proximal tubular epithelium as a urate extrusion pump. Polymorphisms of *ABCG2* may contribute to a “pseudo-overproduction” phenotype due to reduced UA intestinal excretion.¹¹ ABCG2 expression has been found to be upregulated in partially nephrectomized rats, and SUA levels were unaltered by the change in renal function.¹² This suggests that SUA homeostasis may be maintained in the context of renal impairment by means of upregulated intestinal excretion via ABCG2.

Our understanding of urate homeostasis is still evolving as multiple other urate transporters have been identified in recent years, such as NPT1 (nicotinate phosphoribosyltransferase; encoded by the *SLC17A1* gene).¹³

Definition of Hyperuricemia

Age- and sex-related normative ranges for serum urate exist, although cut-off values do vary among studies, thus hindering comparison of results. Hyperuricemia is typically defined as serum urate concentration > 6.0 mg/dL (> 360 μ mol/L) in women, > 7.0 mg/dL (> 415 μ mol/L) in men and > 5.5 mg/dL (> 330 μ mol/L) in children and adolescents.¹⁴ The fractional excretion of filtered urate (FEU) is higher in children (15–30%) compared to adults (10%).¹⁵ This accounts for a linear increase in serum urate levels up to the age of 15 years. The uricosuric effect of estrogens leads to lower serum urate levels in premenopausal women. Following menopause, however, urate levels tend to be more comparable to those of males of similar age.

A serum urate concentration of 7.0 mg/dL (415 μ mol/L) is defined as the upper limits of normal, as it approaches the limits of urate solubility within water. Urate is more soluble in plasma than urine, and crystal deposits may form in the soft tissues and joints when urate exceeds solubility limits, often at concentrations exceeding 10.0 mg/dL (600 μ mol/L). These urate crystals form as monosodium urate (MSU). Multiple factors have been identified that may contribute to an increased risk of MSU crystallization.¹⁶

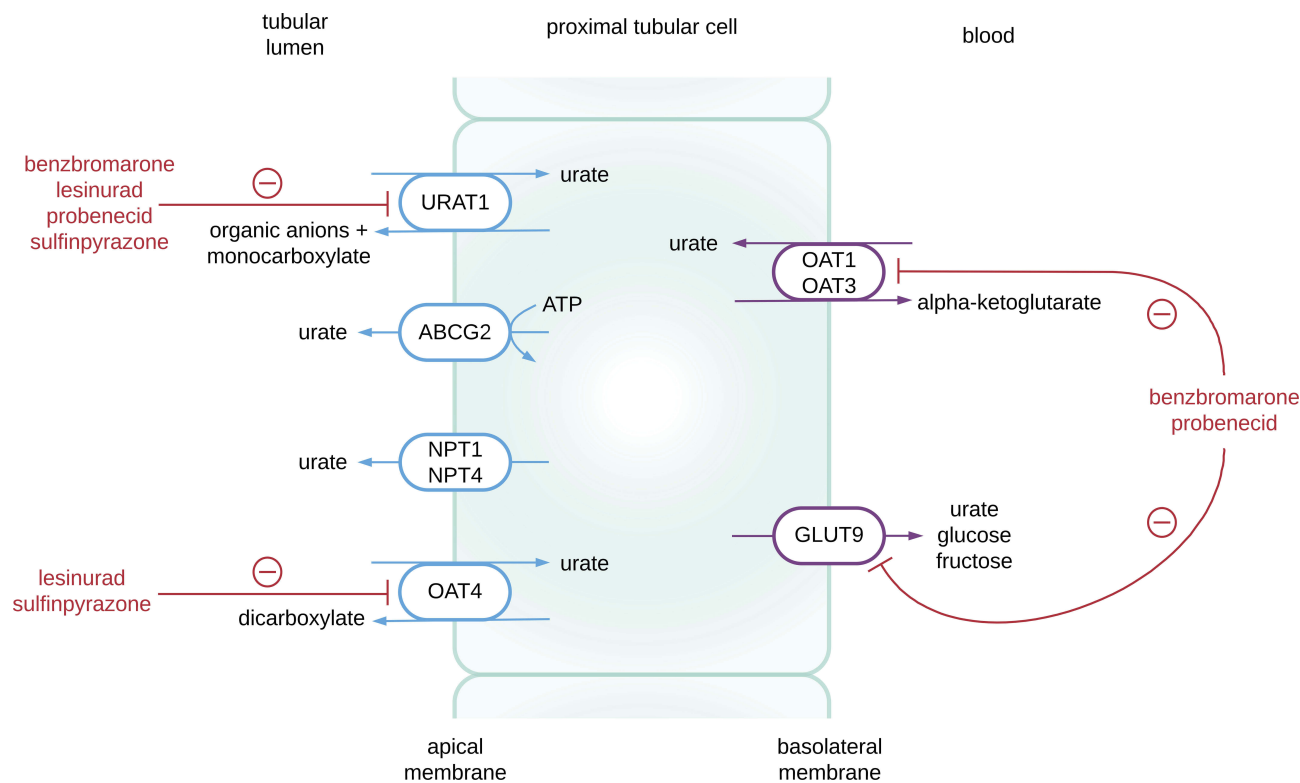


Figure 2 Renal urate transporters. Urate reabsorption is mediated by the proximal tubular apical transporters URAT 1 and OAT4, and the basolateral transporter GLUT 9. Urate secretion is mediated by the apical transporters ABCG2, NPT1, NPT4, and the basolateral transporters OAT1 and OAT3. Benzbromarone and probenecid act as inhibitors of URAT 1, OAT1, OAT 3 and GLUT9. Lesinurad and sulfipyrazone inhibit URAT 1 and OAT4.

Most humans excrete urine that is supersaturated with UA. As the urinary pH is more variable than that of blood, the ratio of UA to urate varies considerably. At lower urinary pH, there will be a greater proportion of undissociated UA compared to urate. In the context of urinary acidification, there is a predisposition for UA urinary crystallization to occur that may contribute to the development of nephrolithiasis.¹⁷

Biological Actions of Uric Acid

The majority of mammalian species have low levels of circulating UA as it is converted by the enzyme uricase (urate oxidase) to the highly soluble compound allantoin. Uricase is situated in the hepatocyte peroxisomes. Humans, and some of the other higher primates, lack the ability to produce uricase due to the presence of two truncating mutations in the uricase gene that introduce premature stop codons.¹⁸ Humans are therefore exposed to relative hyperuricemia.

In the extracellular environment, UA is one of the strongest antioxidant compounds alongside ascorbate.¹⁹ Indeed, UA plays a role in preventing lipid peroxidation although ascorbate must be present for this to occur.²⁰

Consequently, reduced oxidative stress is a hypothesized evolutionary advantage to the relative hyperuricemia present in humans.²¹ In experimental models, UA has been found to act as a peroxynitrite scavenger in neuronal cells, diminishing the transport of leukocytes across the blood brain barrier.²² Hyperuricemia may offer a neuroprotective advantage in neurodegenerative diseases such as Alzheimer's disease,²³ Parkinson's disease,²⁴ and multiple sclerosis.²⁵ In rats, UA has been associated with reduced production of the free radical nitrotyrosine by hepatocytes during hemorrhagic shock, and its administration leads to attenuated liver tissue injury.²⁶ High SUA levels in patients with atherosclerosis have been correlated with elevated total serum antioxidant capacity, and are proposed to play a compensatory role in reducing vascular oxidative damage.²⁷ UA is present in the respiratory epithelial lining fluid where it contributes to antioxidant defenses. After accounting for potential confounders, hypouricemia in smokers has been attributed to higher rates of chronic obstructive pulmonary disease (COPD) and lung cancer.²⁸ Urate may also play an immunological role by acting as a "danger signal" when released from dying cells. In doing so, it may help activate CD8 cells and

facilitate apoptotic recognition by dendritic cells.²⁹ Furthermore, it has been theorized that the uricase mutation acts to create an evolutionary advantageous “thrifty gene” that maintains BP in the setting of low dietary salt intake, and may help boost body fat stores when faced with food scarcity.^{30,31} Increased proximal tubular reabsorption of sodium has been demonstrated in hyperuricemic individuals, suggestive of the metabolic changes seen in those with hyperinsulinism.³²

Despite these proposed benefits, urate is known to act as a pro-oxidant and pro-inflammatory mediator within the intracellular environment. Multiple *in vitro* biochemical effects have been described including activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase.³³ The resultant superoxide generation by phagocytes stimulates the release of ROS which contribute to oxidative stress. Other effects include upregulation of pro-inflammatory transcription factors, vasoconstrictive factors and chemokines, which may induce proximal tubular dysfunction^{34,35} as well as vascular smooth muscle proliferation.^{36,37} Urate acts to induce both mitochondrial and endothelial dysfunction.^{38,39} The infusion of UA into humans has been associated with increased interleukin 6 (IL-6) levels in response to an oral lipid challenge which may help explain increased cardiovascular risk in those with subclinical hyperuricemia.⁴⁰ Furthermore, it has been associated with impaired endothelial nitric oxide (eNO) release and impaired acetylcholine-induced forearm vasodilation.⁴¹ Conversely, evidence suggests that hypouricemia may be associated with deleterious physiological effects. Extremely low levels of urate (e.g. < 1.0 mg/dL [$< 60 \mu\text{mol/L}$]) have been linked with increased risk of cardiovascular events in a J-shaped distribution in adults.^{42–44}

The hypothesis regarding the antagonistic pro- and anti-oxidant effects of UA has been described in the literature as the “oxidant-antioxidant paradox”.⁴⁵ This may help explain the mixed and contradictory results of studies whereby hyperuricemia is induced *in vivo* via UA infusion. Under certain conditions, particularly the hydrophilic environment, the protective effects of UA are manifested. Whether extracellular UA is always associated with beneficial effects requires further research. What remains clear is that UA demonstrates different physiological properties within different biological systems and biochemical environments.

Etiology of Hyperuricemia

A range of factors have been identified that may contribute to increased hyperuricemia risk. These can be broadly classified into factors associated with increased purine

synthesis and/or urate production, versus factors that inhibit urate excretion and clearance. These are summarized in Table 1. The latter is a more common cause of secondary hyperuricemia and can be exacerbated by volume depletion and the use of diuretic medications (both loop and thiazide diuretics), as hypovolemia leads to compensatory UA proximal tubular reabsorption.

A small number of individuals with hyperuricemia have inherited defects resulting in primary overproduction of UA. Genetic deficiency of HPRT is associated with Lesch-Nyhan syndrome, an X-linked recessive disorder characterized by hyperuricemia and self-mutilating behaviours. Other monogenic causes of hyperuricemia include phosphoribosylpyrophosphate synthetase (PRS) superactivity and adenine phosphoribosyltransferase (APRT) deficiency.⁴⁶

The exogenous pool of UA is determined by dietary intake and may be boosted by purine rich foods. However, as stated above, dietary purines only contribute to a small proportion of total body UA generation.^{3,47} Evidence suggests that total protein intake does not correlate with hyperuricemia risk.⁴⁸ Furthermore, intake of dairy,⁴⁸ caffeine^{49,50} and vitaminC^{51,52} may be inversely associated with hyperuricemia risk.

The percentage increase in the consumption of fructose in the Westernized diet over the past four decades, particularly from high-fructose corn syrup added to sugar-sweetened beverages, has been linked to an increased incidence of hyperuricemia, as well as obesity.^{53–55} Although fruits contain natural fructose, their ability to induce hyperuricemia is believed to be offset by a combination of other intrinsic properties of the fruit, including the presence of fibre (which slows intestinal absorption of UA), vitamin C (which provides an antioxidant effect and enhances urinary UA excretion), catechins and flavonoids (which both offer further antioxidant effects).⁵⁶ Fructose is known to activate the hepatocyte fructokinase pathway. The depletion of ATP in this pathway leads to increased purine turnover.⁴⁸ XO-mediated disposal of purines occurs, and UA is generated as a terminal product. Intracellular accumulation of UA contributes to mitochondrial oxidative stress, leading to fructose generation via the aldose reductase pathway, and further fructokinase upregulation. There is controversy as to whether GLUT9 may function as both a fructose and urate transporter, thus being responsible for urate reabsorption in the context of increased fructose intake.^{57,58}

Evidence suggests that hyperuricemia risk may be partially programmed *in utero*. Preeclampsia is associated with increased maternal and fetal SUA levels, believed to

Table 1 Etiology of Hyperuricemia

Increased Purine Synthesis and/or UA Production (~10% of Cases)	Decreased UA Excretion (~90% of Cases)
<p>Clinical disorders</p> <ul style="list-style-type: none"> ● Obesity and insulin resistance ● Increased cell turnover <ul style="list-style-type: none"> ○ Myelo- and lymphoproliferative disorders ○ Hemolytic disorders ○ Malignancy ○ Severe proliferative psoriasis ○ Paget's disease ● Tissue ischemia/hypoxia (e.g. myocardial infarction, status epilepticus) ● Down syndrome 	<p>Clinical disorders</p> <ul style="list-style-type: none"> ● Renal insufficiency ● Small bowel disease ● Volume depletion (e.g. hypovolemia, heart failure) ● Diabetic ketoacidosis ● Lactic acidosis ● Preeclampsia ● Obesity ● Hyperparathyroidism ● Hypothyroidism ● Sarcoidosis
<p>Genetic disorders - inborn errors of metabolism</p> <ul style="list-style-type: none"> ● Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) ● Phosphoribosylpyrophosphate synthetase superactivity ● Glycogen storage diseases - type I (glucose-6-phosphatase deficiency), III, V and VII 	<p>Genetic disorders</p> <ul style="list-style-type: none"> ● Uromodulin pathogenic variants secondary to autosomal dominant tubulointerstitial kidney disease ● Genetic polymorphisms in genes encoding urate transporters: <i>SLC2A9</i> (GLUT9), <i>SLC22A12</i> (URAT1), <i>ABCG2</i>, <i>SLC17A1</i> ● Glomerulocystic kidney disease
<p>Diet-induced</p> <ul style="list-style-type: none"> ● Ethanol ● Excessive dietary purine ingestion (e.g. seafood, fatty meats, dried beans/legumes/peas, certain vegetables) ● Fructose ● Vitamin B3 (niacin) ● Vitamin B12 deficiency 	<p>Diet-induced</p> <ul style="list-style-type: none"> ● Ethanol ● Salt restriction and dehydration ● Starvation ketoacidosis
<p>Drug- or toxin-induced</p> <ul style="list-style-type: none"> ● Cytotoxic agents → leading to tumour lysis syndrome ● Acadesine (4-amino-5-imidazole carboxamide riboside) 	<p>Drug- or toxin-induced</p> <ul style="list-style-type: none"> ● Diuretics (thiazide and loop) ● Calcineurin inhibitors (cyclosporine and tacrolimus) ● Low-dose salicylates ● Beta blockers ● Ethambutol ● Pyrazinamide ● Levodopa ● Methoxyflurane ● Laxative abuse → leading to alkalosis ● Lead → leading to nephropathy (saturnine gout) ● Beryllium → leading to chronic beryllium disease

occur secondary to endothelial dysfunction and reduced glomerular filtration rate (GFR).^{59,60} Maternal hyperuricemia during pregnancy is known to contribute to placental dysfunction, leading to intrauterine growth restriction (IUGR), increased risk of salt-sensitive hypertension, vascular disease, reduced nephron number, and increased risk of hyperuricemia in the offspring.^{30,61} The risk of these outcomes is particularly increased in the context of gestational hypertension and proteinuria.⁶² Twin studies and genetic epidemiological techniques estimate that there is

considerable heritability with regards to SUA levels, ranging from 40% to 73%.^{63–65} Genome wide association studies (GWAS) have identified single nucleotide polymorphisms (SNPs) at 28 genomic loci implicated in UA regulation, accounting for an estimated 6.0–7.7% of SUA variability.^{66,67}

Epidemiology of Hyperuricemia

United States epidemiological data from 2007 to 2008 suggest that the prevalence of hyperuricemia in the adult

population is as high as 21.4% and this continues to increase over time.⁶⁸ Within the US population, the prevalence is marginally higher in African Americans than those from other ethnic groups (25.7% versus 22.1%). Italian data also suggest increasing prevalence between the years 2005 to 2009 (from 8.5% to 11.9% of the population respectively) using a cut-off SUA value of 6.0 mg/dL (360 μ mol/L).⁶⁹ The highest prevalence of hyperuricemia worldwide has been described in the Taiwanese aboriginal population with rates of 41.4%.⁷⁰ Factors that may be contributing to increased hyperuricemia prevalence include the aforementioned change in dietary patterns, increased life expectancy, increased rates of obesity, and the increased availability of certain medications (particularly diuretics).

Hyperuricemia and Its Relationship with Disease

The relationship between hyperuricemia and disease is evidenced most clearly with gout⁷¹ and nephrolithiasis, but epidemiologic associations with heart failure (both with and without preserved ejection fraction),^{72,73} insulin resistance and components of the metabolic syndrome,^{74,75} atherosclerosis,⁷⁶ endothelial dysfunction,⁷⁴ acute and chronic renal impairment, and hypertension have been reported, despite an inability to infer direct causality. The specific links with hypertension will be discussed in detail later in this review.

Hyperuricemia and Overall Cardiovascular Risk

Longitudinal data from the National Health and Nutrition Examination Survey (NHANES) demonstrates that total and cardiovascular mortality correlates with SUA levels in both sexes over 10 years of follow up. From the lowest to the highest SUA quartile, there was a significant increase in cardiovascular mortality rates from 3.1 to 7.8 per 1000 person-years.⁷⁷ This association remained statistically significant even after adjustment for multiple comorbidities. Evidence from the European Study on Cardiovascular Risk Prevention and Management in Daily Practice (EURIKA) study suggests that SUA levels are positively associated with 10-year risk of cardiovascular mortality in patients without evidence of cardiovascular disease but with at least one cardiovascular risk factor (i.e. dyslipidemia, hypertension, smoking, diabetes or obesity).⁷⁸ Even SUA levels within the upper normal range have been attributed to

increased cardiovascular risk.^{79,80} Studies have looked at the role of allopurinol in reducing cardiovascular risk in those with hyperuricemia. A meta-analysis by Higgins and colleagues identified favorable improvement in markers of vascular health for those treated with XO inhibition.⁸¹ Furthermore, allopurinol use has been associated with reduction in left ventricular mass.⁸² Overall, there is a wealth of data to suggest SUA acts an independent risk factor for cardiovascular disease whilst also acting as a risk factor for other factors that may influence cardiovascular risk such as hypertension, obesity and insulin resistance. Indeed, the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study demonstrated that the effect of SUA on total and cardiovascular mortality outweighed that of age or BP.⁸³

Hyperuricemia and Kidney Disease

Elevated SUA is recognized not just as a biomarker for cardiovascular, but also for renal, morbidity. The relationship with chronic kidney disease (CKD) is complicated by the fact that reduced GFR is, in turn, associated with increased SUA levels secondary to reduced renal clearance. In experimental models, this has been somewhat counter-balanced by a compensatory increase in intestinal excretion of UA in the setting of renal insufficiency.^{12,84}

Hyperuricemia can be implicated in the development of acute kidney injury (AKI), either via crystal-dependent or other independent mechanisms. The former is typically a complication of tumour lysis syndrome whereby tubular obstruction occurs due to crystal deposition within the tubular lamina.⁸⁵ AKI in this context is associated with significant mortality, and prophylactic rasburicase (recombinant uricase) may help mitigate this risk.⁸⁶ Studies have demonstrated that in post-operative patients, elevated SUA levels increase the risk of AKI in a mechanism that is crystal-independent.^{87,88} The proposed mechanisms by which UA may induce both renal and cardiovascular injury will be explored later but include a pro-inflammatory response and endothelial dysfunction.

Large scale trials including the German Chronic Kidney Disease (GCKD) study⁸⁹ and NHANES⁹⁰ showed that the age-standardized prevalence of hyperuricemia and gout increases with decline in GFR. In those with established CKD, there is limited evidence to suggest that SUA levels predict progression of disease except in certain groups including those with diabetic nephropathy and IgA nephropathy.^{91,92} However, SUA levels have been demonstrated to predict the development of CKD in

those with normal renal function, as summarized by Johnson and colleagues.⁹³ Furthermore, a large scale prospective trial of 21,475 healthy individuals followed for a median of 7 years demonstrated that SUA levels in the range 7.0–8.9 mg/dL (415–535 $\mu\text{mol/L}$) were associated with a doubling of the risk of incident CKD (estimated GFR [eGFR] < 60 mL/min/1.73m²), and levels \geq 9.0 (\geq 540 $\mu\text{mol/L}$) were associated with a tripling of the risk, after adjusting for baseline eGFR.⁹⁴ This study supports an independent association between hyperuricemia and the subsequent development of new onset kidney disease.

As will be discussed later in this review, hyperuricemia is a known independent risk factor for hypertension, as well as the metabolic syndrome and glomerular proteinuria.⁹⁵ These are risk factors which may, in turn, lead to progression of CKD.⁹⁶ Pediatric data has demonstrated that, in those with an eGFR < 60 mL/min/1.73m², the prevalence of hyperuricemia is 70%, compared with 34% in a control group with eGFR > 60 mL/min/1.73m². There was noted to be close correlation between SUA and BP in the group with stage 3–5 CKD, and this group were more likely to be hypertensive.⁹⁷ Data from the CKiD group has also highlighted that, in children and adolescents, hyperuricemia may act as a risk factor for faster progression of CKD.⁹⁸ Studies have suggested potential roles for UA-lowering therapies (allopurinol⁹⁹ and febuxostat¹⁰⁰) in slowing GFR decline. However, the use of febuxostat in adults with asymptomatic hyperuricemia and stage 3 CKD failed to demonstrate a protective effect on progressive renal impairment compared with placebo.¹⁰¹

The Link Between Hyperuricemia and Hypertension

Historical Observations

An association between hyperuricemia and hypertension was postulated as far back as 1879 where a relationship between “gouty families” and elevated BP was noted.² Not long after, Haig made the link between SUA and multiple comorbidities including hypertension.¹⁰² However, due to lack of data to suggest a direct association, SUA was widely believed to act as a surrogate marker for comorbidities such as diabetes, kidney disease and obesity. The clinical relevance of SUA was therefore largely disregarded.

In the 1960s, the link between SUA and BP was revisited and slowly gained greater recognition. Studies noted that 25–47% of adults with untreated hypertension were hyperuricemic.^{103,104} This figure rose to 75% in those with

malignant hypertension.¹⁰³ In 1972, the Israeli Heart Trial demonstrated that for young males (aged 17 to 25 years) within the highest tertile for SUA measurement, there was a two-fold increase in risk of hypertension after 5 years of follow up.¹⁰⁵ This association has since been described worldwide across different ethnicities including African American, Asian American and Japanese populations.^{106–111}

Epidemiological Studies Demonstrating Association

Over the past three decades, there has been an increasing appreciation that hyperuricemia is a strong independent predictor of hypertension and may indeed be causative. In 1994, Jossa and colleagues reported an independent association between SUA levels and the development of hypertension in 619 Italian males over 12 years of follow up; where age, BMI, serum cholesterol and serum triglyceride levels were controlled for.¹¹² In more recent years, a host of clinical trials have demonstrated comparable findings.^{113–117}

In 2011, Grayson and colleagues published a systematic review of 55,607 patients in 18 prospective cohort studies.¹¹⁸ They identified that for every 1 mg/dL (60 $\mu\text{mol/L}$) increase in UA levels, the pooled relative risk for incident hypertension was 1.13 (95% CI 1.06–1.20) after accounting for potential confounders. This risk was more pronounced in females and younger individuals. Another cohort study of 15,143 subjects identified a similar risk for incident prehypertension with a 9% increased risk for those with SUA levels in the fourth quintile of the population, and 17% risk for those with levels in the fifth quintile, compared with those in the bottom quintile.¹¹⁹ Cicero and colleagues selected 619 individuals from the Brisighella Heart Study and found a significant incremental increase in risk of hypertension and metabolic syndrome, along with an increase of carotid intima media thickness (CIMT), in those progressing from the second to fourth quartile of SUA measurement (from 23% to 56.3% for hypertension prevalence).¹²⁰ These were otherwise healthy individuals (mostly adults) without known cardiovascular disease. In participants of the Generation 3 Framingham cohort with mean age of 40 years, SUA was significantly associated with measures of arterial vascular stiffness, including carotid-femoral and carotid-radial pulse wave velocities (CF-PWV and CR-PWV).¹²¹ This data was supported by a more recent study showing SUA to be an independent associating factor for CF-PWV after adjustment for SBP/DBP, BMI and gender.¹²² A retrospective cohort study looking at 3,584 prehypertensive Japanese adults

found that the cumulative risk of progressing from prehypertension to hypertension over a 5 year period was significantly higher in those with hyperuricemia (30.7% versus 24.0%).¹²³ This study, however, only looked at single assessment of office BP and did not assess repeat measurements or 24 hr ambulatory BP. In 2045 adult participants of the PAMELA study, a large Italian longitudinal epidemiological study on blood pressure, SUA was found to independently predict both new onset home and ambulatory hypertension. The risk increased 34% and 29% respectively for an increase in SUA of 1 mg/dL (60 μ mol/L).⁸³ As alluded to previously, this SUA increase was associated with a fully adjusted increase in risk of cardiovascular and all-cause mortality (22% and 12% respectively).

With regards to an association with age, hyperuricemia (> 6.8 mg/dL [410 μ mol/L]) has been found to predict refractory hypertension in females \geq 65 years (odds ratio 3.11, 95% CI 1.06–9.1) independent of CKD, although this association was not found in males.¹²⁴ Lee and colleagues assessed the relationship between SUA, BP and age in a cohort of 45,908 Korean adults who had never been on either UA-lowering or antihypertensive therapies. The association was not significant in those \geq 60 years of age, but was present below this age threshold, and was noted to be stronger in females.¹²⁵ In men < 60 years, hyperuricemia increased the relative risk of hypertension by approximately 30%, and in women < 40 years, this risk was elevated 2.6 fold. More recent data from the same group showed a positive association between SUA and incident hypertension (specifically increase in DBP) over a mean follow up of 3.3 years in those < 55 years of age (relative risk 1.74 per 1.0 mg/dL [60 μ mol/L] of SUA) compared with those \geq 55 years.¹²⁶ Similar findings were reported by Forman and colleagues in 745 males from the Health Professionals' Follow-up Study where the relative risk of incident hypertension for 1-SD increase in SUA (i.e. 1.25 mg/dL [75 μ mol/L] increase) was 1.38 in those younger than 60 years and 0.9 in those \geq 60 years.¹²⁷ Epidemiological data thereby suggests an age-dependent weakening of the association between SUA and BP.

Multiple studies support a stronger association between SUA and hypertension in those of younger age. The Moscow Children's Hypertension Study and the Hungarian Children's Health Study were the first to describe this association in detail, despite much lower incidence of hyperuricemia in this younger cohort.^{128,129} These trials found that hyperuricemia strongly correlated with hypertension but they did not control for diagnoses independent of UA levels, such as known

renal, cardiovascular and endocrine disease. This therefore impeded the generalization of results. In the former study, hyperuricemia (> 8.0 mg/dL [$>$ 480 μ mol/L]) was present in 9.5% of normotensive adolescents, 49% of those with borderline hypertension, and 73% of those with moderate to severe hypertension. The latter study followed 17,634 children over 13 years and found that hyperuricemia, early sexual maturity and elevated heart rate were all risk factors for developing hypertension.

Essential hypertension has been reported in 89% of children and adolescents with UA levels > 5.5 mg/dL (> 330 μ mol/L), compared with 30% in those with secondary hypertension and 0% in healthy controls or those diagnosed with white-coat hypertension.⁷⁹ These differences in SUA could not be accounted for by variability in GFR. The relationship between SUA levels and both SBP and DBP was continuous, and SBP relationship was stronger than that reported in adults ($r=0.8053$).¹³⁰ A study of 501 children and adolescents (aged 6–18 years) referred for cardiovascular risk assessment found that for each 1 mg/dL (60 μ mol/L) increase in SUA level, the risk of having prehypertension or hypertension increased by at least 50% over normotensive children.¹³¹ This study controlled for factors including puberty, gender, BMI and renal function. The National Survey 1999–2006 demonstrated that among 6036 US adolescents (aged 12–17 years), 34% had SUA levels > 5.5 mg/dL (\geq 330 μ mol/L) and these individuals had a twofold increased risk for hypertension (defined as SBP/DBP \geq 95% for age, sex and height) compared with those in a lower SUA range.¹³² The Bogalusa Heart Study followed 577 child and adolescent patients, divided into white and black ethnicity, over an average of 12 years and found that elevated childhood UA levels were associated with increased BP beginning in childhood, with higher BP persisting into adulthood. This trend was noted in both ethnic groups and in both genders.¹¹³ A Korean longitudinal birth cohort looked at a much younger cohort of pre-school children. They followed 449 children and identified that SUA levels at 3 years of age were associated with SUA levels at 5 and 7 years. Those with elevated SUA (above the median) at 3 years of age had a significant increase in SBP and DBP compared with those who had SUA levels below the median. Additionally, elevated SUA levels at both 3 and 5 years of age had a cumulative effect in causing a significant elevation of SBP at 7 years of age.¹³³ SUA and purine metabolites were measured in 246 children from the Dutch KOALA Birth Cohort Study. Higher DBP was related to higher ratios of UA/xanthine and xanthine/hypoxanthine, which can be interpreted as proxy markers of UA

production.¹³⁴ The conclusion from this study is that SUA production may have a causal role in raising DBP, an indicator of increased systemic vascular resistance and a risk factor for cardiovascular disease in younger individuals.¹³⁵ In 539 adolescents with type 2 diabetes mellitus (T2DM) recruited to the TODAY study, elevated SUA (≥ 6.8 mg/dL [≥ 410 $\mu\text{mol/L}$]) at baseline was present in a large proportion (25.6%) of the cohort and it was an independent risk factor for incident hypertension and albuminuria over 7 years of follow up, after controlling for baseline eGFR and insulin sensitivity.¹³⁶

In adults with essential hypertension, SUA has been found to be a strong independent predictor of a nocturnal non-dipping BP profile.¹³⁷ Non-dipping of BP overnight by the normal 10–20% seen in normotensive individuals, as assessed by ambulatory BP monitoring (ABPM), is known to be associated with greater risk of cardiovascular, cerebrovascular and renal disease.^{138,139} Additionally, increased SUA levels were independently associated with abnormal circadian BP variability (BPV), also assessed by ABPM, in 300 patients with untreated essential hypertension.¹⁴⁰ BPV, which includes concepts such as “white-coat hypertension” or “masked hypertension”, is recognized as a risk factor for end organ damage, as well as cardiovascular and cerebrovascular morbidity and mortality.^{141–143} The conclusion from these studies is that SUA may therefore predict a more pathogenic BP profile in those with established hypertension. In 6984 adults (mean age 50.3) with treated hypertension, no relationship was found between SUA levels and long-term BP control, although higher UA levels were associated with longitudinal decline in GFR, and with increased cardiovascular risk in women.¹⁴⁴

Han and colleagues recently sought to address the temporal relationship between hyperuricemia and hypertension.¹⁴⁵ They conducted a longitudinal study of 17,044 Chinese adults and, using a novel statistical approach in the form of a cross-lagged path analysis, surmised that hyperuricemia leads to hyperinsulinism which then contributes to the development of hypertension. Despite this conclusion, the relationship demonstrated was still an association without evidence of causality, and multiple sources of confounding were identified.¹⁴⁶ Several studies have demonstrated a possible role for prehypertensive or hypertensive states in inducing hyperuricemia, and have sought to explain the mechanism by which this may occur. Early hypertension is known to reduce renal blood flow via the development of microvascular damage. Evidence suggests that this impairs renal excretion of urate and increases UA synthesis secondary to local tissue ischemia.^{147–149} This has been

supported by evidence that angiotensin II and norepinephrine infusions in normotensive subjects induce hyperuricemia, reduce renal perfusion and raise BP, with reversibility observed upon discontinuation of the infusions.¹⁵⁰

Genetic Studies

Mendelian randomization analysis in two Danish cohorts sought to investigate genetic polymorphisms in the *SLC2A9* gene (responsible for urate reabsorption via GLUT9), the primary genetic determinant of SUA levels. This study's results contrasted with observational findings and could not identify a causal association between hyperuricemia secondary to *SLC2A9* variants and the risk of developing hypertension or ischemic heart disease.¹⁵¹ Body mass index (BMI) was, however, implicated as a potential confounder and was independently associated with cardiovascular risk.

A meta-analysis of GWAS analysed the results of 28,283 Caucasian individuals and identified SNPs at 8 genetic loci (*ABCG2*, *GCKR*, *PDZK1*, *R3HDM2-INHBC* region, *RREB1*, *SLC17A1*, *SLC22A11*, *SLC2A9*) demonstrating statistically significant genome-wide association with SUA levels, and 2 of these loci (*ABCG1* and *SLC2A9*) achieved significant association with gout risk. A “genetic urate score” was created based on the effect of the most significant SNP at each locus. This was strongly associated with SUA levels and gout (odds ratio 12.4 per 1.68 mg/dL [100 $\mu\text{mol/L}$]). However, there was found to be no association with BP, fasting glucose, eGFR, CKD (defined as $\text{eGFR} < 60$ mL/min/ 1.73m^2) or coronary heart disease (CHD) in this cohort.⁶⁶ These results were reproduced in the Women's Genome Health Study (WGHS) cohort.

A smaller study in a Japanese cohort assessed polymorphisms within the *XDH* gene and found that these may contribute to a phenotype predisposed to hypertension, atherosclerosis and CKD. This effect is postulated to be secondary to interference with circulating nitric oxide reductase which may in turn affect levels of ROS and thereby increase cardiovascular morbidity.¹⁵²

Genetic data suggest a complex interplay of factors between UA expression and the development of cardiovascular disease. The inability to establish direct causality between hyperuricemia secondary to genetic polymorphisms and the risk of hypertension does, however, need to be interpreted with caution as epigenetic factors may play an important role in gene expression over the course of a lifetime, and alternative biochemical pathways, such as fructose metabolism, affect UA levels

independent of the genetic expression of urate transporters. GWAS have characteristically looked at SUA levels and cardiovascular risk in adult populations but have excluded children and adolescents. Results may not be generalizable to the general population given that they typically look at cohorts of shared ethnicity. Furthermore, many of the cardiovascular outcomes in these cohorts are dependent on patient self-reporting, and data on the use of UA-lowering treatment within cohorts are also inconsistent.

Pre-Clinical Studies

Although the extrapolation of results from animal and in vitro models poses multiple challenges, an array of studies have sought to explore the pathogenic etiology for hypertension secondary to hyperuricemia. In 1913, Desgrez demonstrated that the injection of UA into rabbits led to a direct increase in BP.¹⁵³ More recently, animal studies using rats have established that inducing mild hyperuricemia using oxonic acid, a uricase inhibitor, can induce hypertension after a short period of 3 weeks.¹⁵⁴ Concurrent treatment with either allopurinol (a XO inhibitor) or benzbromarone (a uricosuric agent) lowered SUA levels and prevented the development of hypertension. This mechanism was independent of urate crystal formation as renal biopsies were normal by light microscopy.

A two-step model, divided into acute and chronic phases, has been recognized as a potential explanation for the development of elevated BP due to hyperuricemia:

1. Acute phase - hypertension in these experimental models has been attributed to an initial acute UA-dependent phase with an increase in juxtaglomerular renin release and a decrease in macula densa NO synthase production within the kidney. UA has been demonstrated to impair phosphorylation of endothelium-derived nitric oxide (eNO) via activation of UA transporters.¹⁵⁵ The resultant increase in circulating ROS, and increased oxidative stress in the macula densa, leads to an ischemic-type endothelial injury identified on renal biopsy. This injury is independent of crystal formation.^{154,156,157} This phase results in renal vasoconstriction that is independent of salt intake and reversible with the use of UA-lowering medications and renin-angiotensin-aldosterone system (RAAS) blockade. Notably, losartan has a role as both an angiotensin II blocker and a uricosuric agent.¹⁵⁸ Benzbromarone, irbesartan and losartan

have all been found to diminish the effect of UA on eNO suppression.¹⁵⁵

2. Chronic phase - after prolonged hyperuricemia, a chronic phase of injury occurs that is associated with inflammatory microvascular changes predominantly affecting the afferent arterioles. There is uptake of UA into vascular smooth muscle cells (VSMC) via URAT1, resulting in activation of proinflammatory mediators such as monocyte chemoattractant protein-1 (MCP-1) and increased cyclooxygenase-2 (COX-2) mRNA expression.¹⁵⁹ The resultant VSMC injury leads to progressive afferent arteriopathy and interstitial inflammation, believed to be independent of UA levels. It mimics the progression of salt-sensitive hypertension that is seen in humans and is unresponsive to UA-lowering treatment.¹⁶⁰ Murine knockout models have demonstrated that loss of uricase and *SLC2A9* can contribute to hypertension and metabolic syndrome, as well as premature mortality.^{161,162} However, as humans lack the uricase enzyme, the extrapolation of these results should be interpreted with caution.

Another animal model using knockout mice with deletion of hepatocyte-specific GLUT9 found that induced hyperuricemia (with the use of inosine) was not linked with hypertension despite the development of mild renal impairment.¹⁶³ In hepatocytes, GLUT9 acts as a urate transporter to provide urate to the hepatocyte enzyme uricase. This study suggested a lack of direct causality between urate and BP in mice. Again, the lack of uricase in humans leads us to query the direct applicability of such findings.

Rat models have linked high fructose-containing diets with insulin resistance, hypertension, hypertriglyceridemia, and fatty liver disease,¹⁶⁴⁻¹⁶⁶ and similar findings have been demonstrated in humans.¹⁶⁷ In rats, fructose is noted to cause an elevation in BP at the time of consumption but this effect is not sustained and this may be due to the effect of the uricase enzyme which helps to metabolize SUA.¹⁶⁸ Fructose's role in inducing metabolic syndrome and hypertension has been addressed by Nakagawa and colleagues.¹⁶⁹ They found that allopurinol and benzbromarone were both effective in preventing or reversing features of metabolic syndrome in rats within an 8 week period, and allopurinol successfully prevented fructose-induced systolic hypertension, as well as hyperinsulinism, hypertriglyceridemia and weight gain.

Therapeutic Management of Hyperuricemia and Effects on BP Control

In both younger and older age groups, UA-lowering therapies have been used to test the association between SUA levels and BP. These agents include XO inhibitors (e.g. allopurinol), non-purine analogue inhibitors of XO (e.g. febuxostat) and uricosuric agents (e.g. benzbromarone, benzbromarone, ethebencid, probenecid, sulfapyrazone, zoxazolamine). Rasburicase is licensed for use in the treatment of acute hyperuricemia such as that induced by chemotherapy. A list of these medications is summarized in Table 2.

A number of trials have demonstrated beneficial effects of allopurinol, possibly independent of its UA-lowering properties. Allopurinol has been associated with improvement in vascular endothelial function, as measured by forearm venous occlusion plethysmography, in elderly patients with chronic heart failure,¹⁷⁰ in heavy smokers¹⁷¹ and in type 2 diabetic patients.¹⁷² These effects have been

attributed to reduction in vascular oxidative stress with observed improvement in forearm blood flow. Probenecid use did not induce similar effects, thus raising the question as to whether urate itself actually plays a direct role in endothelial dysfunction.¹⁷⁰ It is proposed that the beneficial effects of allopurinol may be related to a reduction in ROS production by the blocking of XO, and that urate itself may not be the direct causative agent for hypertension. Indeed, in healthy controls, UA infusion was not associated with acute evidence of endothelial dysfunction¹⁷³ and has also been found to improve endothelial function in patients with type 1 diabetes and smokers, suggesting that elevated UA concentrations in vivo may be protective for those with pre-established cardiovascular risk.¹⁷⁴ A significant short-term lowering of SUA with uricase in patients with T2DM was not found to have a direct vascular effect thus suggesting that there is no causal link between elevated SUA concentrations and endothelial dysfunction.¹⁷⁵ However, uricase depletes UA via conversion to allantoin and, in doing so, increases the production of ROS which would be expected

Table 2 Uric Acid Lowering Therapies

Drug	Mechanism of Action	Additional Information
Allopurinol	XO inhibitor	Metabolized to oxipurinol which reversibly inhibits XO. Renally excreted and dose should be adjusted for renal function
Febuxostat	XO inhibitor	A non-purine selective XO inhibitor. Hepatically excreted but contraindicated for those with CKD stages IV-V
Topiroxustat	XO inhibitor	Hepatically excreted; licensed for use in Japan
Oxipurinol	XO inhibitor	Active metabolite of allopurinol
Benzbromarone	URAT1 inhibitor	Brominated analogue of benzbromarone. Also inhibits OAT1/2/3 and GLUT9
Benzbromarone	As for benzbromarone	–
Ethebenecid	As for probenecid	No longer in production
Lesinurad	URAT1 inhibitor	Also inhibits OAT4
Probenecid	URAT1 inhibitor	Also inhibits OAT1/3 and GLUT9, Acts to inhibit the renal excretion of multiple drug types including penicillins and NSAIDs
Sulfapyrazone	URAT1 inhibitor	Also inhibits OAT4
Zoxazolamine	Uricosuric agent – mechanism unknown	Previously used as a central muscle relaxant although withdrawn due to risk of hepatotoxicity
Rasburicase	Recombinant urate oxidase	For prophylaxis and treatment of acute hyperuricemia. Metabolizes uric acid to allantoin
Pegloticase	Recombinant urate oxidase	Pegylated in order to extend the half-life. Can be given every 2 to 4 weeks via infusion
Other drugs with known uricosuric effects include losartan and fenofibrate		

Abbreviations: XO, xanthine oxidase; URAT1, urate transporter 1; OAT, organic acid transporter; GLUT9, glucose transporter 9; CKD, chronic kidney disease; NSAIDs, nonsteroidal anti-inflammatory drugs.

to have a pro-inflammatory effect, and would diminish extracellular UA levels thus limiting the antioxidant effects of UA.

With regards to BP control, allopurinol has been found to lower brachial and central BP and reduce the risk of progressive CIMT in patients without hyperuricemia following ischemic stroke and transient ischemic attack (TIA).¹⁷⁶ However, there was no observed difference in markers of endothelial dysfunction, such as von Willebrand factor (vWF) and soluble intercellular adhesion molecule 1 (s-ICAM-1), in those treated with allopurinol versus placebo. In those with modestly elevated SUA concentrations (6.0–6.2 mg/dL [360–370 $\mu\text{mol/L}$]), allopurinol has been demonstrated to lower SBP and DBP in middle-aged overweight and prehypertensive adults over a period of 8 weeks.¹⁷⁷ Kanbay and colleagues demonstrated a reduction in 24 hr systolic ambulatory BP, along with an increase in eGFR, in patients with asymptomatic hyperuricemia treated with allopurinol for 4 months.¹⁷⁸ These patients did, however, experience significant reduction in SUA levels. Recent RCTs have been unable to find associations between allopurinol use and change in endothelial-dependent vasodilation,¹⁷⁹ kidney-specific or systemic RAAS activity (measured as change in renal blood flow response to captopril, and plasma renin and angiotensin II activity),¹⁸⁰ and an improvement in BP with adjuvant use of allopurinol in those already on thiazide diuretics as first-line treatment for hypertension.¹⁸¹ A meta-analysis looking at 738 individuals, most of whom were adults, found that allopurinol was responsible for a small reduction in both SBP (3.3 mmHg) and DBP (1.3 mmHg) compared with controls.¹⁸² Evidence suggests that older hypertensive adults (> 65 years) require higher doses of allopurinol to achieve a greater reduction in BP,¹⁸³ and those treated with higher doses also have significantly lower risk of cardiac and cerebrovascular events.¹⁸⁴ However, recent studies looking at cohorts with mean age of 64¹⁸⁵ and 67¹⁸⁶ years respectively have demonstrated contradictory findings and have not found significant changes in BP control with the use of allopurinol, febuxostat or benzbromarone. In the LIFE study, losartan's use as an antihypertensive agent was associated with lower risk of cardiovascular morbidity and mortality compared with atenolol, and this may be secondary to its adjunctive role as a uricosuric agent.¹⁸⁷ The use of pegloticase, a recombinant uricase conjugated to polyethylene glycol, has been explored for the treatment of gout refractory to standard treatment or where standard treatment is contraindicated. Significant reductions in SBP

and DBP were found in the group receiving pegloticase on a biweekly basis who maintained SUA levels < 6.0 mg/dL (< 360 $\mu\text{mol/L}$) throughout the study period and these effects were independent of alterations in eGFR.¹⁸⁸ Of note, pegloticase does not inhibit XO and this is therefore contradictory evidence to suggest that SUA may have a direct effect on BP control.

On the basis of the aforementioned experimental studies, it is postulated that subjects with hyperuricemia who have not had hypertension long enough to develop secondary VSMC arteriolar injury could benefit most from UA-lowering therapy. Feig and colleagues performed a crossover trial in 30 adolescents (aged 11–17 years) with newly diagnosed hypertension and SUA levels \geq 6.0 mg/dL (\geq 360 $\mu\text{mol/L}$).¹⁸⁹ Allopurinol was compared with placebo for 4 weeks in each arm of the trial and they found that 20 of the 30 adolescents achieved normal BP by casual and ambulatory criteria whilst taking allopurinol compared with 1 participant taking placebo. Soletsky and colleagues looked at 4-week treatment with either allopurinol or probenecid compared with placebo and found a BP reduction in prehypertensive obese adolescents (aged 11 to 17 years). There was a significant reduction in both SBP and DBP, by 10.2 mmHg and 9.0 mmHg respectively, compared with placebo.¹⁹⁰ In a randomized open-label trial of 42 adolescents with essential hypertension aged 12–19 years, allopurinol used in combination with enalapril was found to be more effective than allopurinol alone in reducing BP and reducing SUA levels. All patients had baseline SUA levels \geq 5.5 mg/dL (\geq 330 $\mu\text{mol/L}$) and 37% of the cohort were overweight or obese.¹⁹¹

A Cochrane review in 2017¹⁹² looking to determine whether the use of UA-lowering therapies lowers BP in hypertensive patients identified only 3 randomized controlled trials (RCTs) that met inclusion criteria, including the aforementioned trials by Feig and Soletsky.^{189,190} The third multicenter trial included 109 adults (aged \geq 18 years) with primary hypertension.¹⁹³ The use of febuxostat, compared with placebo, was evaluated over 6 weeks. No significant difference between the febuxostat and placebo groups was found in ambulatory daytime or nighttime BP, or clinic SBP or DBP, from baseline to week 6. There was however a reduction in SBP in the subgroup analysis of hypertensive and hyperuricemic patients with normal renal function. The conclusion of this systematic review was that there is low quality of evidence to establish that UA-lowering therapies reduce BP. When assessing BP via 24 hr ABPM, there was no significant reduction in either SBP (–6.2 mmHg, 95% CI –12.8 to 0.5) or DBP (–3.9 mmHg, 95% CI –9.2 to 1.4).

This was despite high quality evidence showing that these therapies do effectively reduce SUA levels (by 3.1 mg/dL [185 μ mol/L] [95% CI 2.4 to 3.8]).

Data from both NHANES 1999–2004¹⁹⁴ and 2003–2006¹⁹⁵ support an epidemiological association between fructose intake and hypertension in the US population. Fructose is associated with acute elevation of BP in healthy young adults and this effect was not observed with glucose intake.¹⁹⁶ Reduction of SBP and DBP has been demonstrated prospectively in those who reduced their consumption of sugar-sweetened beverages.¹⁹⁷ In adult males receiving 200 g of fructose per day for 2 weeks, there was an increase in fasting SUA levels with elevation of both SBP and DBP obtained via 24 hr ABPM recordings. Allopurinol was found to lower SUA and prevent the increase in daytime SBP and DBP that was seen in the control group.¹⁶⁷

Whether the management of hyperuricemia may represent a new frontier in the optimization of BP control has still not been fully expounded and large-scale RCTs are lacking. The use of UA lowering therapies, particularly in younger age groups, requires further evaluation. At present, the side effect profile of UA-lowering agents limits their widespread use. In particular, allopurinol is associated with dose-related adverse effects that range from a relatively common rash to rarer effects such as aplastic anemia and severe hypersensitivity reactions (reported in 0.38% of patients).¹⁹⁸ Renal insufficiency may predispose to the build-up of oxypurinol, the major metabolite of allopurinol, which increases the risk of potentially life-threatening reactions.¹⁹⁹ Concurrent use of ACE inhibitors and allopurinol may also raise the risk of potentially lethal skin reactions such as toxic epidermal necrolysis.²⁰⁰ Probenecid can affect the renal excretion of other drugs (such as captopril, NSAIDs and penicillins) and its uricosuric effect may induce nephrolithiasis.²⁰¹ Furthermore, there is no current evidence to suggest that any of the UA-lowering therapies alone are more effective at lowering BP than traditional antihypertensive agents.

Conclusion

SUA is an independent risk factor for incident hypertension but there still remains a lack of concrete evidence to support the therapeutic lowering of UA in order to treat or prevent hypertension, or to reduce the risk of cardiovascular, cerebrovascular or renal disease. It is postulated that XO inhibitors would be of greater benefit than uricosuric agents in reducing this risk as they both lower SUA and

block the production of pro-inflammatory ROS. In the management of hyperuricemia, there is also a role for the development of novel therapies that could target the multiple urate transporters that have been identified to date. At present, we lack a true understanding of the temporality of the relationship between SUA and BP, and the specific effect of SUA on endothelial function versus that of ROS generated by purine metabolism. Genetic studies suggest factors, notably BMI, may act as confounders and that causality cannot be inferred.

Large scale, prospective, double blind RCTs are required to look at specific UA-lowering therapies to assess if they can be used to treat hypertension, or if they can alter the progression from prehypertensive to hypertensive states. There is considerable evidence to suggest that the relationship between SUA and hypertension is lost with increasing age and with duration of hypertension. The role of UA-lowering therapies in different age groups needs to be evaluated fully as those of younger age may benefit the most if the two-step pathogenic hypothesis is to be believed.

Disclosure

The authors report no other conflicts of interest in this work.

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