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# Hypertension and Hyperuricemia

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## Abstract

Essential hypertension affects about 25% of the world population and is considered as a major causal factor of myocardial infarct, congestive heart failure, stroke, end-stage renal disease and also risk factor for type 2 diabetes. Hypertension is implicated in 13% of deaths globally. The essential hypertension is a multifactorial and complex disease and the number of contributory factors in its etiology are increasing each year as being appreciated in recent decades. Recent experimental and clinical studies in animals and humans have implicated uric acid in the early onset mechanism of essential hypertension in children and adolescents. An association exists also between uric acid, cardiovascular diseases and mortality, metabolic syndrome, subclinical atherosclerosis, stroke, kidney diseases, type 2 diabetes and endothelial dysfunction. Asymptomatic hyperuricemia was also a strong risk factor for resistant hypertension in the elderly. Epidemiological data suggest that hyperuricemia and gout is becoming more prevalent worldwide, probably as the consequence of Westernization of diet and life style, obesity and the increased availability of certain medications. These data suggest that the prevalence of hyperuricemia in the adult population is 20%-40% and this continues to increase over time.

The aim of this article was to review the results of the most recent studies about the possible relation between elevated uric acid levels and the

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onset or worsening of hypertension and other cardiovascular, renal and metabolic diseases.

All these studies support a role for high serum uric acid levels (>6mg/dl or 60mg/l) in hypertension–associated morbidities and should bring attention to physicians in regard to their patients. The relationship between serum uric acid and hypertension is lost with increasing age and with duration of hypertension.

The regular physical exercise, Mediterranean diet and decreased consumption of beverages with high fructose corn syrup may lower the risk for hypertension. It is postulated that xanthine oxidase inhibitors would be of greater benefit than uricosuric agents in reducing the cardiovascular, renal and cerebral risk as they both lower serum uric acid and block the production of proinflammatory reactive oxygen species (ROS). Urate lowering therapy is associated with normalization of both serum uric acid and blood pressure in younger population. In contrast, in older hypertensive population, urate lowering therapy have minimal effects on blood pressure but appear to improve cardiorenal endpoints.

**Keywords:** Hypertension, uric acid, hyperuricemia, risk.

## INTRODUCTION

Uric acid (UA) is a weak and final production of purine mononucleotide catabolism which means that cannot be further metabolized. In other mammals UA is degraded by uricase into allantoin, which is a more soluble substance. Unfortunately, uricase during Miocene was lost in humans. This loss of function provided supposedly some evolutionary advantages.

Firstly, UA acts as an antioxidant of the plasma. It can scavenge single oxygen, peroxyl and hydroxyl radicals, reacts with peroxynitrite and stabilizes endothelial nitric oxide synthase (eNOS) activity. Its antioxidant effects need the presence of ascorbate.

Secondly, UA increases salt sensitivity and may have maintained BP in the poor salt environment of these early times.

Thirdly, UA increases fat storage and lipogenesis. Fruits contain more fructose at the end of the summer, resulting in an enhanced lipid deposition to better cope with the nearby winter. Fructose corn syrup is the only sugar which can raise UA level. It is metabolized in the liver by the phosphofructokinase in fructose-1- phosphate (F1P). F1P will be converted into glucose, glycogen, lactate and lipids which step consumes a large amount of adenosine triphosphate (ATP), resulting in substrates for the purine metabolism (1).

UA is the last product of purine metabolism. The last two steps of the pathway are catalyzed by the xanthine oxidoreductase (XOR) which exists under two interconvertible isoforms: the xanthine dehydrogenase (XDH), which uses nicotine adenine dinucleotide (NAD+) as an electron acceptor, and xanthine oxidase (XO), which uses oxygen as an electron acceptor (2).

Only the XO is able to create reactive oxygen species (ROS) during the generation of UA. This latter form is more activated during ischemia, extensive surgery and stress, and is mainly present in the liver, the intestine and the vascular wall (3). UA acts as a strong antioxidant compound in the extracellular environment but has pro-inflammatory effects within the intracellular area. XO-related oxidative stress may decrease nitric oxide (NO), increase oxidative stress in the macula densa, induce endothelial and mitochondrial dysfunction, renal vasoconstriction, activation of rennin-angiotensin system (RAS), vascular smooth muscle cell proliferation and in chronic phase of hyperuricemia lead in interstitial renal fibrosis and arteriosclerosis. In early stage hyperuricemia increases blood pressure (BP) by high reabsorption of Na+ in renal tubes and it is urate lower therapy (ULT) depended but in late stage the micro renal injury causes salt sensitive kidney – hypertension depended. These studies revealed that hypertension (HT) develops in two steps (4). At the physiological pH of 7.40 in the extracellular compartment, 99% of uric acid is in ionized form as urate (as monosodium urate in blood and calcium, potassium and ammonium in urine). Urate is more soluble in plasma than in urine. The lower pH in urine can favorize the crystals formation. (2)

The physiological daily amount of endogenous and exogenous uric acid is about 700mg, which is balanced by an equal output via urine and feces. About 25-30% of uric acid is broken down by intestinal flora and excreted in the stool, while 65-75% is excreted through the kidneys. The majority of circulating uric acid is free in plasma and is readily filtered by the glomeruli, but up to 90% may be reabsorbed. UA homeostasis is governed by the balance between the rate of UA generation (determined by purine catabolism), renal excretion, and intestinal secretion. Multiple urate transporters have been identified as playing a role in renal tubular reabsorption and secretion of urate and intestinal secretion, thus helping regulate homeostasis (URATE 1, GLUT9, ABCG2 and recent one NPTI). These transporters are encoded respectively by the genes (SLC22A12, SLC2A9, ABCG2, SLC17A1) (5).

Purines can be synthesized endogenously or can derive from dietary sources. Hypoxanthine and Xanthine are the intermediate products of this catabolism. 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 fatty meat, seafood and alcohol. (4)

Normal serum UA levels range between 2.4 to 7 mg/dl (180 to 415 μmol/l) in temperature 37˚and neutral pH, but age- and sex-related normative ranges for serum UA exist, too. Hyperuricemia is typically defined as SUA concentration > 6.0 mg/dL (> 360μmol/L) in women, >7.0mg/dL (>415μmol/L) in men and >5.5mg/dL (> 330 μmol/L) in children and adolescents. (2)

The uricosuric effect of estrogens leads to lower SUA levels in premenopausal women. Following menopause, however, urate levels tend to be more comparable to those of males of similar age.

A serum UA concentration of 7.0 mg/dL (415 μmol/L) is defined as the upper limits of normal, as it approaches the limits of UA water solubility. The gold standard is to maintain UA < 6.0mg /dl in hyperuricemic patients (1).

Reduced UA excretion is a common cause of hyperuricemia and found in renal failure and in the presence of insulin resistance, in part due to an increased renal reabsorption under the effect of high insulin levels. Loop and thiazide diuretics reduce renal UA excretion. Other clinical disorders may reduce the UA excretion such as: obesity, small bowl disease, hyperparathyroidism, hypothyroidism, preeclampsia, sarcoidosis, volume depletion, etc. Genetic polymorphism in urate transporter one (URAT-1) and Glut 9 transporter can also result in hyperuricemia. A small number of individuals with hyperuricemia have inherited defects resulting in primary overproduction of UA (5).

**The history of link between hypertension and hyperuricemia**

The strong association between hyperuricemia and hypertension has been recognized as far back as 1879, where a relationship between “gouty

families" and elevated blood pressure was noted (6).

Gout is one of the oldest recognized disease in humans, described by Hippocrates as ″arthritis of the rich″ due to its association with animal food and alcohol, but a documented history dates back to the Egyptians in 2640 BC.

Haig in 1890 made the link between of (UA) and multiple comorbidities including HT (7). Due to the lack of data to suggest a direct association, it was believed that UA acts as a marker for comorbidities such as diabetes, kidney disease and obesity.

Studies conducted between 1950 and 1960 evidenced that 25%–47% of adults with untreated hypertension were hyperuricemic (8, 9, 10). This prevalence rose to 58% among those receiving diuretics and to 75% in those with malignant hypertension (9).

In 1972, the Israeli Heart Trial demonstrated that for young males (aged 17 to 25 years) within the highest tertile for the plasma UA measurement, there was a two-fold increase in risk of hypertension after 5 years of follow up (11). This association has been described worldwide across different ethnicities including African American, Asian American and Japanese populations (12, 13, 14, 15, 16).

Klein et al. one year later demonstrated a linear relationship between serum uric acid (SUA) level and systolic blood pressure (SBP) in both white and black people (17). Since then, many epidemiological studies showed a strong association between UA and HT and particularly the risk of developing HT.

In 2011, Grayson and colleagues published a systematic review and meta-analysis of 18 prospective cohort studies of 55,607 patients (18). They revealed that a 1 mg/dl increase in UA level was associated with an increased risk of incident HT by 13% (pooled RR = 1.13). These effects were significantly larger in women and in younger population studies especially in those with metabolic syndrome (14). Therefore, UA is often considered as an independent factor for HT, especially earlier in the life course than at a later stage (18, 19, 20). With regards to an association with gender and age, hyperuricemia (> 6.8 mg/dL [410 μmol/L]) has been found to predict refractory hypertension in females ≥ 65 years (odds ratio 3.11, 95% CI 1.06–9.1) independent of chronic kidney disease (CKD), although this association was not found in males (21).

In a cohort of 45,908 Korean adults who had never been on either ULT or antihypertensive therapies, in the 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 (22). More recent data from the same group showed a positive association between SUA and incident hypertension {specifically increase in diastolic blood pressure, (DBP) } over a mean follow up of 3.3 years in those < 55 years (relative risk 1.74 per 1.0 mg/dL [60 μmol/L] of SUA) compared with those ≥ 55 years (23). The conclusion from one 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 (24). The relationship between SUA levels and both SBP and DBP was continuous, and SBP relationship was stronger in adults (25). 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 (26, 27). These trials, found that hyperuricemia was strongly correlated with hypertension. Hyperuricemia (> 8.0 mg/dL [> 480 μmol/L]) was present in 9.5% of normotensive adolescents, 49% of those with borderline hypertension, and 73% of those with moderate to severe hypertension. Essential hypertension has been reported in 89% of children and adolescents with UA levels > 5.5 mg/dL (> 330 μmol/L), compared with 30% in those with secondary hypertension and 0% in healthy controls or those diagnosed with white-coat hypertension (28).

In a short-term crossover study involving adolescents with newly diagnosed hypertension, treatment with 200 mg allopurinol twice a day resulted in reduction of SUA levels, which was associated with a suppression of HT in 20 out 30 patients treated (29). This supports the concept that an early intervention aiming to prevent hypeuricemia may be beneficial regarding HT and its comorbidities. In a prospective trial, 113 patients with estimated eGFR<60ml/min/1.73m² and hyperuricemia were randomized to receive allopurinol 100 mg/day or to continue their usual therapy. After 23 months, SUA level was reduced in 6mg/dl in Xanthine oxidase (XO) inhibitor group but was unchanged in control group. The e GFR value was not significantly changed in allopurinol group but it was worsened in the control group, suggesting that lowering SUA by XO inhibitors is expected to slow the progression of renal disease (30). Other two studies achieved positive impact of XO inhibitors (febuxostat) versus placebo in hypertensive and/or hyperuricemic patients. It was estimated that after four years, for every 1mg/dl reduction of SUA level, there would be a preservation of 1.15ml/min/1.73m² of eGFR (31), and after six months with SUA in 6mg/dl, was showed a reduction of plasma renin and aldosterone concentrations with a significant increase eGFR (+5.5%, p=0.001) (32).

Importantly, nowadays, according to a recent meta-analysis, there is still a lack of evidence to recommend the use of allopurinol or other uric acid lowering therapy as a treatment of HT (33). Xanthine oxidase not only generates UA but also produces superoxide. The increase of SUA may be due to the activation of XO and any benefit observed with blocking XO is more likely due to the XO associated oxidants rather from lowering UA. Allopurinol can also reduce fructose-induced proinflammatory mechanisms (monocyte chemoattractant protein-1 synthesis). This explain why XO inhibitors have been found

to improve endothelial function in contrast to probenecid, but more data are needed (34). A protective effect of UA on coronary arteries has been shown in isolated perfused hearts in the 1980s 2. Conversely, early UA infusion after an acute ischemic stroke did not improve functional outcomes at 90 days (35).

Choi and colleagues analyzed a cohort of 24.768 people with newly diagnosed gout and 50.000 matched control and found that use of calcium channel blockers and losartan was associated with a moderately lower risk of incident gout among patients with HT (36). LIFE study confirmed the same for uricosouric capacity of losartan. In contrast, the use of diuretics, β-blockers, ACE inhibitors and non-losartan angiotensin II receptors blockers was associated with an increased risk of incident gout among patients with HT (37).

These results contrast with a Mendelian randomization studies, which investigate genetic polymorphisms in the SLC2A9 gene (responsible for urate reabsorption via GLUT9), the primary genetic determinant of SUA levels, where no evidence for causal associations between UA and ischemic heart disease or blood pressure (BP) was found. Body mass index (BMI) was implicated as a potential confounder (5, 38).

Genome wide association studies (GWAS) analyzed the results of 28,283 Caucasian individuals and identified single nucleotide polymorphisms (SNPs) at 8 genetic loci demonstrating statistically significant genome-wide association with SUA levels, and 2 of these loci (ABCG1 and SLC2A9) achieved significant association with gout risk, estimated 6.0–7.7% of SUA variability. There was found to be no association with BP, fasting glucose, eGFR, chronic kidney disease (defined as eGFR < 60 mL/min/1.73m2) or coronary heart disease (CHD) in this cohort (39, 40).

However, it is important to note that Mendelian studies involve gene-dependent association, and even though hyperuricemia has an important genetic component (40% to 73%) (41), it is primarily caused by life habit and diet, and alternative biochemical pathways, such as fructose metabolism, affect UA levels.

Prolonged fructose consumption may therefore contribute to the development of metabolic syndrome by increasing circulating concentration of UA, Gama Glutamyl Transferase (GGT) activity and productions of adipokine retinol binding protein-4(RBP-4) (41). Increased circulating concentration of RBP-4 have been linked with increased visceral adiposity and have been shown to directly contribute to hepatic insulin resistance via induction of hepatic glucose production and impairment of insulin signaling in muscle. (16)

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. The hypothesis regarding the antagonistic pro- and antioxidant effects of UA described in the literature as the “oxidant-antioxidant paradox”

may help explain the mixed and contradictory results of studies. What remains clear is that UA demonstrates different physiological properties within different biological systems and biochemical environments. 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 arteriolar injury could benefit most from ULT but the side effect profile of ULT 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. (38).

## CONCLUSION

The relationship between SUA and HT is lost with increasing age and with duration of HT. The regular physical exercise, Mediterranean diet and decreased consumption of beverages with high fructose corn syrup may lower the risk for HT. It is postulated that XO inhibitors would be of greater benefit than uricosuric agents in reducing the cardiovascular, renal and cerebral risk as they both lower SUA and block the production of proinflammatory ROS. Urate lowering therapy is associated with normalization of both SUA and BP in younger population. In contrast, in older hypertensive population, ULT have minimal effects on BP but appear to improve cardiorenal endpoints.

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