THE ROLE OF URIC ACID IN HYPERTENSION, CARDIOVASCULAR EVENTS, AND CHRONIC KIDNEY DISEASE
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Introduction
Following discovery by Mahomed and Garrod in the early 1800s that hyperuricaemia was the cause of gout, it was proposed that it also had a causal role in a variety of cardiovascular and renal conditions, including hypertension, arteriosclerosis (the histological lesion of hypertension), kidney disease, and heart disease [1]. By the 1990s, however, prospective studies could not establish uric acid as a causal factor in these conditions [2].

In the early 2000s, a substantial body of clinical, epidemiological, and animal studies have coherently defined the actions of uric acid with cardiovascular events (CVD) in the general population and, particularly, among hypertensive patients.

Definition of serum urate levels
Serum uric acid levels are similar in boys and girls during childhood. However, a gender difference appears at adolescence. In normal healthy adult males, serum urate values exceed those in females of reproductive age due to enhanced renal urate clearance by oestrogen metabolism [3]. After menopause, serum urate values in healthy females increase and approximate those in healthy males of corresponding age. In postmenopausal women, treatment with hormone replacement therapy causes a lesser rise in serum urate values [4].

Serum urate values may vary significantly as a result of factors that modify its generation or urinary excretion. High purine or protein diets, alcohol consumption, high cell turnover, or enzymatic defects of purine metabolism enhance generation, while reduction in glomerular filtration rate (GFR) or administration of diuretics (such as thiazide) decrease urinary excretion of uric acid. As a result, serum uric acid levels are increased. On the other hand, drugs that interfere with purine metabolism or enhance increased urinary excretion are associated with a reduction in serum uric acid levels.

Urate is generally defined as serum levels > 6.5-7 mg/dl and > 6 mg/dl in men and women, respectively [5].

Homoaetosis of uric acid
Uric acid is a weak, odourless organic acid. Its solubility is poor at acid pH but is greatly enhanced at higher pH values due to its conversion to the anion urate. Under normal conditions, urate is freely filtered at the glomerulus as only 5% is reabsorbed by the kidney. As a result, most uric acid circulates as urate anions. Normal humans have serum urate concentrations approximating the thermodynamic solubility of uric acid in plasma (about 6.8 mg/dl) and excrete urine that is supersaturated with respect to uric acid.

Uric acid is not typically ingested. It is produced in the liver from the degradation of dietary and endogenously synthesized purine precursors. Dietary intake appears to provide a significant source of urate precursors [6].

The normal adult male has a total body urate of about 1200 mg, twice that of the female. Consequently, the urate generation and excretion constant is higher in men than in women [5].

Renal urate excretion accounts for about 2/3 of the uric acid turnover. Four distinct processes are involved in the renal handling of urate: 1) glomerular filtration; 2) post glomerular reabsorption; 3) proximal tubular reabsorption; and 4) post proximal tubular secretion and reabsorption in the cortical collecting duct. Inorganic phosphate reabsorption is a major contributor of urate excretion [5].

The remaining 1/3 of urate load is excreted through the gastrointestinal tract. Urate enters the gut by passive diffusion where it is completely degraded by colonic bacteria with little being excreted in the stools [5].

Persistent hyperuricaemia can result either from diminished renal excretion or excessive overproduction of uric acid. In 85-90% of individuals reduced uric acid excretion by the kidneys accounts for the elevated serum uric acid levels [7].

Biological effects of uric acid
Several pathophysiological mechanisms linking serum uric acid to cardiovascular damage at the cellular and tissue levels have been proposed. Soluble uric acid (urate) is not an inert molecule, but possesses several biological actions that could be either beneficial or detrimental [5].

Antioxidant properties
One of the beneficial properties of urate is its ability to act as an aqueous antioxidant. Along with ascorbate, urate may be one of the most important antioxidants in the plasma, reacting with a variety of oxidants. In particular, by scavenging superoxide anions, it blocks the reaction of superoxide with nitric oxide and prevents the formation of peroxynitrite, which is a very toxic product to the cells [8, 9].

Uric acid may also prevent the degradation of extracellular superoxide dismutase (SOD), an extracellular enzyme which is critical in blocking the reaction and inactivation of nitric oxide by superoxide anions [5]. It has been postulated that the ability of urate to react with oxidants may be an attempt of the heart to maintain integrity and function of vascular cells in conditions associated with oxidative stress [5].

Deleterious effects
In contrast to its beneficial actions, uric acid has also been found to have a wide variety of deleterious effects on vascular cells.

Endothelial dysfunction. Uric acid may contribute to endothelial dysfunction. Uric acid influxes in healthy humans result in impaired acetylcholine induced vasodilatation in the forearm, documenting impaired endothelial nitric oxide (NO) release. In experimental animals, mild hyperuricaemia inhibits the NO system in the kidney [10]. The mechanism by which uric acid impairs endothelial function may be related to a pro-oxidative action under certain conditions.

Proliferation of vascular smooth muscle cells. Uric acid also stimulates proliferation of vascular smooth muscle cells by activating intracellular protein mechanisms resulting in proliferative and proinflammatory phenotypes, which produce growth factors, vasoconstrictive and proinflammatory molecules [11].

Pathophysiological significance of hyperuricaemia
Epidemiological studies have reported a relation between serum uric acid and a wide spectrum of cardiovascular diseases [12]. This relation is not limited to only elevated serum uric acid levels, but has been reported with uric acid levels within the high normal range [3].

Hypertension
Hyperuricaemia is very common in hypertension. It has been reported in 25-40% of untreated hypertensive individuals, in 50% of those treated with diuretics, and in over 80% of those with malignant hypertension [3]. High serum uric acid levels in hypertensive patients have been attributed to several mechanisms: 1) the reduced renal blood flow that often accompanies the hypertensive state stimulates urate reabsorption in the proximal tubule [3]; 2) the hypertensive microvascular disease leads to local tissue ischaemia, the release of lactate that blocks urate secretion in the proximal tubule and increases uric acid synthesis [13]. Tissue ischaemia leads to ATP degradation to adenosine and xanthine oxidase. Both increased xanthine and xanthine oxidase result in increased generation of uric acid and oxidant (reactive oxygen species) formation, and 3) additional factors can contribute to hyperuricaemia in hypertension such as alcohol abuse, lead intoxication, and diuretic use.

During the past few years, several clinical and experimental studies have indicated that uric acid might be an important factor in the development of primary hypertension. Pathophysiological mechanisms leading to high levels of uric acid can lead to hypertension have been elucidated in experimental animal studies. Rats rendered hyperuricaemia with oxonic acid, an uricase inhibitor, develop hypertension within several weeks [14]. Blood pressure (BP) elevation was shown to be due to uric acid mediated systemic and renal vasoconstriction as a result of activation of the renin–angiotensin system and a reduction in endothelial nitric oxide levels [14]. Renal arterioles are functionally constrained resulting in a decrease in renal glomerular flow, but are structurally normal [14]. At this initial stage, controlling hyperuricaemia with allopurinol, a xanthine oxidase inhibitor or with a uric acid agent prevents or reverses BP elevation and is associated with reversal of abnormal hormonal changes [14].

With persistent and chronic hyperuricaemia, hypertension is associated with the development of preglomerular arthropathy and tubulointerstitial disease, reminiscent of the classic lesions of essential hypertension [15]. Controlling hypertension with diuretics does not prevent the development of microvascular disease. Coupled with reported direct actions of uric acid on endothelial and vascular smooth muscle cells, these observations suggest that uric acid may induce microvascular disease independently of hypertension [15]. At this stage, hypertension becomes salt sensitive and can be controlled with salt restriction. In contrast, withholding uricosuric inhibitor therapy does not reverse the BP elevation [15].

In humans, the link between hyperuricaemia and hypertension has been reported in several studies. Among children newly diagnosed with hypertension, serum uric acid was highly correlated with both systolic and diastolic BP [16]. The Framingham Heart Study indicated that hyperuricaemia preceded the onset of hypertension with an odd ratio of 1.17 for each increase in serum uric acid by 1.3 mg/dl [17]. Similar findings were reported in the Multiple Risk Factor Intervention (MRFIT). In normotensive men without metabolic syndrome, hyperuricaemia (defined as a serum uric acid > 7 mg/dl) was associated with an 89% increased risk of developing hypertension independent of baseline BP measurements, lipid profile, proteinuria, or renal function [18].

In a study involving subjects older than 60 years of age, uric acid did not predict the development of hypertension [19].

Hyperuricaemia is also more common in primary than in secondary hypertension, at least in adolescents [20]. In one study, elevated uric acid levels (> 5.5 mg/dl) were observed in nearly 90% of adolescents with essential hypertension, whereas uric acid levels were significantly lower in those with either secondary hypertension or white coat hypertension. The strength of the linearly synthesized purine relationship between uric acid and hypertension was decreased with increasing patient age and duration of hypertension, suggesting that uric acid may be a more important pathogenetic factor in younger subjects with early onset hypertension [3]. Hyperuricaemia is also common among adults with prehypertension, especially when microalbuminuria is present [21].

Preliminary clinical trials support a role for uric acid in the pathogenesis of early onset primary hypertension. In a double blind, placebo-controlled cross over trial per-
formed in 30 adolescents with hypertension and hyperuricemia, treatment with allopurinol was associated with a significant fall in both casual (measured at the physician's office) and ambulatory BP, and the reduction was similar in magnitude to that achieved with conventional antihypertensive agents [18]. In 205 patients in whom uric acid levels decreased to less than 5 mg/dl (300 μmol/l) during allopurinol therapy, BP became normal in 86%, compared with 3% during the placebo phase of the study [22].

**Cardiovascular disease**

It remains controversial whether uric acid plays a causal role in the development of CVD, or is merely a traditional CVD risk factor. Recent reports from the Framingham Heart Study and Atherosclerotic Risk in Communities (ARIC) study, which collectively involve over 200,000 men and women, claim an association between uric acid and cardiovascular risk [11]. Recent animal studies have suggested that uric acid-induced CVD in multivascular disease. In contrast, other recent studies documented an independent association of uric acid with CVD. In a group of well treated hypertensive patients, the incidence of CVD was significantly increased in patients with high uric acid levels, even with control of other known CVD risk factors including serum creatinine, body mass index (BMI), and diuretic use [24]. Despite blood pressure control, serum uric acid levels increased during treatment and were significantly and independently associated with cardiovascular events [24].

In a population based study, the NHANES I Epidemiologic Follow Up Study, for each increase of 5.9 μmol/l (1 mg/dl) in uric acid the hazard ratio of CVD mortality and ischemic heart disease was increased by 1.16 and 1.3 for men and 1.1 and 1.4 for women, respectively [25]. Results of the LIFE Study provided additional support for an association between baseline uric acid and increased risk of CVD events [25]. Attenuation of the increase in serum uric acid by losartan over 4.8 years reduced CVD events in this high risk population.

**Chronic kidney disease**

Hyperuricemia is highly prevalent in patients with chronic kidney disease (CKD), reflecting reduced efficiency in renal excretion of uric acid and associated with hypouricosuria. The role of uric acid in the initiation and progression of CKD remains controversial. Several epidemiological and experimental evidence suggests a role for uric acid not only as a marker of reduced kidney function but also as a causal risk for the development and progression of renal disease.

Fructose consumption, metabolic syndrome, and risk of cardiovascular disease.

The past few decades have witnessed a major increase in the prevalence of obesity, hypertension, diabetes mellitus, and metabolic syndrome. There is evidence that serum uric acid levels are rising as well. These observations have been associated with a large increase in fructose intake. Fructose is an isomer of glucose synthesized from corn syrup and is currently used as a sweeter in preference to naturally occurring sucrose [29]. Fructose is unique among sugars in that it rapidly causes depletion of ATP and increases both the generation and release of uric acid.

Experimental observations support a link between fructose intake, hyperuricaemia, and hypertension. Rats fed with fructose develop hyperuricemia, hyperuricaemia, metabolic like syndrome, and renal haemodynamic and histological changes very similar to those observed with hyperuricemia [31]. Controlling hyperuricemia with xanthine oxidase inhibitors in these rats partially prevented these changes (Figure 1).


**Figure 1.** Relationship between oxonic acid/fructose induced hyperuricemia, hyperuricemia, and hypertension. CKD: renal failure sensitive (persistent).