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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, arteriolosclerosis (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 convincingly defined a positive association of serum 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 oestrogenic compounds [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 thiazides) 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.

Hyperuricaemia is usually defined as serum levels > 6.5–7 mg/dl and > 6 mg/dl in men and women, respectively [3].

Homeostasis of uric acid

Uric acid (7,9 dihydro-1H-purine-2,6,8(3H)-trione) is a major metabolite of purine nucleotides. In most mammals, purine nucleotides are degraded to xanthine or hypoxanthine through the action of an enzyme complex. In turn, xanthine and hypoxanthine are metabolized to uric acid by xanthine dehydrogenase or urate synthetase and, through urate oxidase, a hepatic derived enzyme, to allantoin which is highly soluble in urine [5].

During the Miocene Period (about 20 to 5 million years ago), two parallel but distinct mutations occurred during the primate evolution rendering the uricase gene non functional, preventing the further oxidation of uric acid to allantoin in humans [5]. This resulted in serum uric acid levels being higher in humans and great apes than in other mammals.

Uric acid is a weak, odourless organic acid. Its solubility is poor at acid pH but is greatly enhanced at high pH dissociating into urate and a hydrogen ion: **uric acid ➔ urate + H^+**

At the normal pH of 7.4, this reaction is shifted to the right. As a result, most uric acid circulates as urate anions. Normal humans have serum urate concentrations approaching the theoretical limit of solubility of urate 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 compounds. 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. Serum urate levels reflect the net balance between its constant production and excretion. Urate is not metabolized by human tissues. To maintain homeostasis, urate is eliminated by the kidney and the gastrointestinal tract [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) presecretory tubular reabsorption; 3) tubular secretion; and 4) post secretory reabsorption. Tubular reabsorption and secretion mechanisms are mediated by a urate/anion exchanger and a voltage sensitive urate channel [5].

Under normal conditions, urate is freely filtered at the glomerulus as only 5% is bound to plasma proteins. Glomerular filtration accounts for only 7–12% of the excreted filtered urate load. After glomerular filtration, uric acid undergoes both pre- and post secretory reabsorption and secretion in the proximal convoluted tubule. Incomplete post secretory reabsorption is a major contributor of urinary excretion of uric acid [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 kidnies 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 (SOD3), 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 host 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 infusions 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 muscles 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 disease (CVD) [12]. This relation is not limited to frankly 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]. The high serum uric acid levels in hypertension 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 (O_2^-) 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 by which 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 constricted resulting in a decline in renal plasma flow, but are structurally normal [14]. At this initial stage, controlling hyperuricaemia with allopurinol, a xanthine oxidase inhibitor or with a uricosuric 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 arteriopathy 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 uricase 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 80% 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 relationship between uric acid level and hypertension 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]. Hypertension 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 hyperuricaemia, 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 most antihypertensive agents [18]. For 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 simply a marker of more traditional CVD risk factors.

Recent reports from the Framingham Heart Study and Atherosclerotic Risk in Communities (ARIC) study, which collectively involve over 200 000 men and women, claim no association between serum uric acid incident CVD in multivariable models [23]. 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 associated with serum uric acid, even with control of other known CVD 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 directly associated with cardiovascular events [24].

In a population based study, the NHANES I Epidemiologic Follow Up Study, for each increase of 59.5 μmol/l (1 mg/dl) in uric acid the hazard ratio of CVD mortality and ischaemic heart disease were 1.09 and 1.17 for men and 1.26 and 1.3 for women, respectively. The 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

Hyperuricaemia 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. Recent 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.

In experimental studies, oxonic acid-induced hyperuricaemia in rats caused the slow development of albuminuria, preglomerular arteriopathy, glomerulosclerosis, and tubulointerstitial disease [14]. Controlling hyperuricaemia with hypouricosuric agents in these animals prevented renal microvascular and histopathologic injury and preserved renal function [14].

Several epidemiological surveys and prospective studies have documented an association between hyperuricaemia and risk of new onset kidney disease. In the Okinawa General Health Maintenance Association study, which included 6400 Japanese participants with normal renal function at baseline, uric acid levels > 8 mg/dl were associated with a 2.9- and 10-fold increased risk of developing CKD (defined as uric acid levels > 1.4 mg/dl in men and > 1.2 mg/dl in women) within 2 years in men and women, respectively [26]. The relationship between serum uric acid levels and incident kidney disease (defined as GFR decrease ≥ 15 ml/min/1.73 m^2 with final GFR < 60 ml/min/ /1.73 m^2) was also evaluated in over 13 000 participants with intact kidney function in two community based cohorts. During a follow-up period of 8.5 years, each 1 mg/dl greater uric acid level at baseline was associated with an approximately 10% increase in risk of kidney disease in multivariable adjusted models.

Chronic use of diuretic therapy has been cited as a possible risk factor for hyperuricaemia induced CKD. Clinical and population based studies have indicated that diuretic usage often accelerates progression to CKD in hypertensive subjects. The use of diuretics in the Syst-Euro, SHEP, INSIGHT, and ALLHAT studies was associated with a greater decline in renal function compared with other treatment groups [3].

In a randomized clinical trial in 54 hyperuricaemic patients with stage 3 or 4 CKD, allopurinol therapy, compared to placebo, during a 1-year follow-up was associated with a significant reduction in serum uric acid levels and delay in progression of CKD (defined as an increase in serum creatinine level > 40% of baseline or the need for replacement therapy) [27]. These interesting observations give support to the hypothesis that hyperuricaemia maybe nephrotoxic in CKD, accelerating progression to ESRD.

In contrast, two other studies failed to substantiate a relationship between serum uric acid levels and CKD. In a separate analysis of 5800 participants from the Cardiovascular Healthy Study (CHS), there was no association between serum uric acid levels and incident CKD defined as eGFR < 60 ml/min/1.73 m^2. Likewise, in a cohort of patients with predominantly nondiabetic stages 3 to 4 CKD, hyperuricaemia was not an independent predictor of progression to end stage renal failure [28].

In gout, whether gouty nephropathy or chronic uric acid nephropathy exists as a specific entity resulting from the direct renal injury from uric acid deposition in renal parenchyma remains controversial but appears to be unlikely. Prior to the advent of hypouricosuric therapy, patients with gout exhibited evidence of CKD (albuminuria, renal functional impairment), hypertension, and histological renal lesions which included arteriolosclerosis, glomerulosclerosis, and tubulointerstitial disease with or without patchy deposition of uric acid crystals in the outer medulla, and were attributed to coexistent hypertension and aging independent of crystal deposition [3].

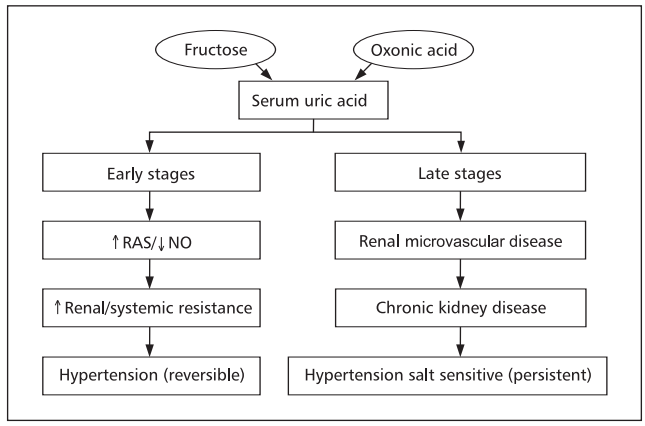

Figure 1. Relationship between oxonic acid/fructose induced hyperuricaemia, hypertension, and CKD; RAS — renin–angiotensin system; NO — nitric oxide

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 dextrose synthesized from corn syrup and is currently used as a sweetener 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 the release of uric acid.

Experimental observations support a link between fructose intake, hyperuricaemia, and hypertension. Rats fed with fructose develop hyperuricaemia, hypertension, metabolic like syndrome, and renal haemodynamic and histological changes very similar to those observed with hyperuricaemia [3]. Controlling hyperuricaemia with xanthine oxidase inhibitors in these rats partially prevented these changes (Figure 1).

Similarly, epidemiological studies have linked fructose intake with increased prevalence of hyperuricaemia, obesity, hypertension, and CKD; features common to metabolic syndrome. There is strong evidence associating fructose intake with hyperuricaemia and increased incidence of gout [30]. However, it is unclear whether fructose intake is causally related to incident hypertension and CKD. Although higher serum uric acid levels are associated with an increased risk of hypertension in younger individuals, several lines of evidence suggest that uric acid may only be a marker of hypertension risk in humans [31]. Large prospective studies in males and females found no association between fructose intake and risk of incident hypertension [31].

An association between fructose intake, hyperuricaemia, albuminuria, and chronic kidney disease has been well documented in several studies. However, a causal relationship between fructose intake and incident CKD remains controversial. Recent analysis of the data of the Atherosclerosis Risk in Communities Study (ARIC) has provided possible answers to these queries. These data suggest that increased fructose consumption is associated with an increased prevalence of CKD mainly in participants with serum uric acid > 9 mg/dl. However, there was no evidence of increased incidence of CKD. These data cast some doubt over the association of fructose intake with the development of hypertension and chronic kidney disease [32].

Conclusions

Serum uric acid, the major metabolite of purine nucleotides, is a recently recognized risk factor for hypertension, CVD, and CKD and may act as a link between metabolic syndrome and the increasing incidence of the newly recognized associated nephropathy.

Reduction of elevated serum uric acid levels may reverse hypertension in adolescents with new onset hypertension and may delay the progression of renal dysfunction in patients with established CKD.

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