Review

Hyperuricemia: A Biomarker of Renal Hemodynamic Impairment

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Abstract

Background: Many epidemiological, clinical, and experimental reports have demonstrated an association between serum uric acid concentration and a variety of cardiovascular and renal diseases, particularly in hypertension. At present, there seems to be no resolution to the question whether this relationship is causal or coincidental. **Summary:** This discussion examines a number of biological, pathophysiological, fundamental, and clinical relationships between serum uric acid concentration and several of these disorders. To this end, discussion and review provide some specific insight conclusions and recommendations related to their clinical relevance. **Key Messages:** We suggest that, in most instances (especially in patients with essential hypertension), the increase in serum uric acid concentration is coincidental, serving as a useful biomarker that relates the magnitude of circulating plasma uric acid concentration with the extent of impaired cardiovascular and renal function. Moreover, the value of certain pharmaceutical agents affecting the serum uric acid level should be considered carefully by taking into consideration the associated pathophysiological derangements.

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Introduction

Uric acid is usually considered for its role in the pathogenesis of gout (i.e. one form of arthritis promoted by hyperuricemia, and urate crystals deposited in joints and other tissues, nephrolithiasis, and nephropathy; tables 1, 2). However, unrelated to crystallization, an elevated serum uric acid concentration has also been associated with a number of cardiovascular and renal diseases including hypertension, atherosclerosis, dyslipidemias, exogenous

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Table 1. Putative relationships of hyperuricemia with human disease and dysfunction

Gout and altered purine metabolism
Altitude
Polycythemia
Aging
Obesity
Stress
Toxemias of pregnancy
Diabetes mellitus
Coronary heart disease
Ischemic heart disease
Reduced renal elimination
Chronic renal disease
Dyslipidemia
Others

Table 2. Hyperuricemia seen in various forms of arterial hypertension

Untreated
Treated (especially diuretics)
Systolic hypertension in the elderly
Large artery stiffness
Renal insufficiency (with hypertension)
Renovascular occlusive disease
Other secondary forms of hypertension

obesity, insulin resistance, and even the aging process. These associations and their functional consequences are the subject of this review.

In the modern era, the association of serum uric acid elevation with essential hypertension began with the report of Stanton and Freis [1] whose first report on this association in 1947 preceded oral diuretic therapy. However, as early as the latter 19th century, Mahomed [2] and later Davis [3] observed in their patients with gout that hyperuricemia may cause hypertension by affecting renal vasculature. However, their notion received no further attention until the report of Stanton and Freis which initiated a plethora of clinical, epidemiological, experimental, and review articles examining this relationship [4–13]. The overwhelming majority of these reports clearly confirmed the association, and it was found that this relationship also existed when uric acid concentration in biological fluids was increased to 'high normal' levels [14]. Hence, the question of whether this relationship is causal or merely 'coincidental' became an issue of considerable controversy. Furthermore, this concern has been extended to another important question: whether asymptomatic hyperuricemia (i.e. in the absence of clinical gout or only incidentally related) should be treated in order to reduce cardiovascular risk or prevent arthritis. This review summarizes and critically evaluates the clinical relevance, conclusions, and recommendations of available reports.

Uric Acid: Biology, Pathophysiology, and Significance

Uric acid is an organic compound that is the end product of purine metabolism in man and higher primates. In other mammals, uric acid is further metabolized to allantoin by the enzyme uricase. During evolution, various mutations in the uricase gene occurred in man rendering the enzyme inactive [15, 16]. As a consequence, plasma uric acid levels are about

10 times higher in human beings (i.e. 5–6 mg/dl in man and 0.5–1 mg/dl in other mammals) [15, 16]. Further, serum uric acid concentration depends on the diet (containing foods rich in purines), degradation of endogenous purines (increased in malignancies, polycythemia, hemolytic anemia, etc.), and its renal excretion [17]. About 70% of uric acid is excreted by the kidneys and, the remaining, by the gastrointestinal tract [17]. Considering the fact that intake and metabolism of purines and their gastrointestinal excretion are fairly constant in most individuals, serum uric acid concentration largely depends upon its urinary excretory function [17]. It should be noted that the renal handling of uric acid is complex and that approximately 90–95% of the renal filtered load is absorbed, mostly by proximal tubules [18]. In man, uric acid secretion by the renal tubules appears to be negligible and, consequently, the excreted amount depends on glomerular filtration and subsequent tubular reabsorption [19]. Since intrarenal hemodynamics affects both processes, it appears to play a dominant role in uric acid elimination [18].

The actual biological role of uric acid is not well defined and has been subjected to various interpretations. From the evolutionary point of view, genetic mutations are generally considered advantageous [20]. In line with this notion is the fact that uric acid is a potent anti-oxidant and is estimated to account for about 50% of the total antioxidant capacity of biological fluids in man [21, 22]. Even more speculatively, the circulating uric acid level in man has been related to higher intelligence and to the regulation of arterial pressure at low dietary salt intake [16, 23]. Furthermore, uric acid has also been suggested to have a neuroprotective action since patients with various neurological disorders, including multiple sclerosis, parkinsonism, and Alzheimer's disease seem to have a significantly lower plasma uric acid concentration than otherwise healthy subjects [24–26].

On the other hand, hyperuricemia clearly has deleterious effects, including gout and related nephrolithiasis, renal damage, and a potential pathogenetic role in a variety of cardiovascular, renal, and other diseases. Thus, it is unclear whether uric acid gene mutations that have occurred during evolution have been advantageous and whether much lower plasma levels of uric acid than presently seen clinically may be sufficient to provide a benefit [21]. Conversely, hyperuricemia potentially related to the diet in developed and industrialized countries may be related to adverse effects [27]. In keeping with this concept are the findings that, in the United States, mean serum uric acid levels have increased gradually from less than 3.5 mg/dl in the 1920s to 6.0–6.5 mg/dl in the 1970s, and possibly even greater in the male than the female gender [11]. Furthermore, diet may influence the epidemiology of hyperuricemia and gout. For instance, since the introduction of Western culture and dietary habits, gout has become endemic among the Maori of New Zealand [27]. Similarly, occurrence of gout was rare among blacks in the United States until the 1940s and 1950s when changes in diet led to the rapid development of various other disorders including obesity, diabetes, hypertension, and currently gout, which have also become more common among blacks in this country than among whites [27]. If correct, this would not be the first example of 'unhealthy' habits annulling beneficial evolutionary changes.

Animal Models of Hyperuricemia and Cardiovascular Disease

As already stated, there is a significant difference in the handling of uric acid between man and other mammals. Consequently, the data obtained from hyperuricemic animals should be interpreted even more cautiously than data from other animal models. At present, the only model that can be labeled as 'naturally occurring hyperuricemia' is the spontaneously hypertensive rat (SHR) [28–30]. The serum uric acid concentration in the SHR is mildly elevated, i.e. double (or higher) that in their predecessors normotensive Wistar-Kyoto (WKY)

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rats (≥1 mg/dl vs. 0.5 mg/dl), and its concentration may be considered elevated in rats but is actually far below the normal level in man [15, 16]. Moreover, when compared with 20-week-old adult WKY rats, hyperuricemic SHRs demonstrated increased arterial pressure and total, renal, and afferent glomerular arteriolar resistances with normal glomerular hydrostatic pressure [31, 32]. Furthermore, they do not exhibit signs of functional (normal serum creatinine level, no proteinuria) or structural (normal histological findings) renal damage [32]. These results suggest that, in SHRs, hyperuricemia is more likely a marker of renal vascular involvement (increased renal vascular and afferent glomerular resistances) than a pathogenetic factor. Significant renal damage occurs in SHRs but only in those older than 60 weeks [33]. In addition to SHRs, we have also examined serum uric acid blood levels in other hypertensive rat models (i.e. DOCA-salt and malignant hypertension induced by the nitric oxide synthase inhibitor, L-NAME) [9, 28, 30]. In those studies, the relation between serum uric acid level with renal and intrarenal hemodynamics in otherwise untreated rats and given various antihypertensive therapies were analyzed [18]. We have consistently found that the serum uric acid level was directly related to renal vascular and afferent glomerular arteriolar resistances and inversely related to renal and single-nephron plasma flow [18]. In keeping with the concept that serum uric acid is primarily a renal hemodynamic marker is our finding that, in L-NAME/SHR rats, the aldosterone receptor antagonist eplerenone did not affect uric acid concentration [34]. This finding could be attributed to the fact that eplerenone had no renal and glomerular hemodynamics effects, although it ameliorated proteinuria and renal histopathological alterations.

Other models involve animals in which various procedures that increase serum uric acid concentration were used. Among the first hyperuricemic models are uricase gene knockout mice that develop a severely increased serum urate level, obstruction of renal tubules with urate crystals, renal failure, and a high mortality rate [35]. Since they quickly developed obstructive nephropathy, these animals are not suitable to study other possible adverse effects of uric acid.

Experimental hyperuricemia may also be induced by treating rats with an inhibitor of urate oxidase, oxonic acid, which prevents conversion of uric acid to allantoin [10, 36]. By selecting an appropriate dose of oxonic acid, it is possible to induce mild hyperuricemia without causing crystal formation. Thus, Sprague-Dawley rats given 2% dietary oxonic acid developed mild hyperuricemia (1.7–3.0 mg/dl), hypertension, and renal injury characterized by interstitial inflammation and fibrosis [36]. In addition, these rats also developed glomerular hypertension [37], afferent glomerular arteriolar nephropathy [38], and glomerular hypertrophy [39]. The associated increased arterial pressure and renal structural changes were prevented by reducing the serum uric acid concentration with either allopurinol (a xanthine oxidase inhibitor) or benziodarone (a uricosuric agent), suggesting that uric acid was a causative factor. Further confirmation that uric acid was the culprit in this setting was the finding that hydrochlorothiazide normalized arterial pressure without affecting either serum uric acid levels or arteriolar damage [38].

Several hypotheses regarding the mechanisms of the adverse effects of uric acid, including hypertension and renal disease, have been proposed. For example, hyperuricemia may affect arterial pressure by activating the renin-angiotensin system and reducing nitric oxide synthase activity [38, 40, 41]. Furthermore, the mechanism of arteriolar disease has also been elucidated through an elaborate intracellular pathway whereby increased uric acid level ultimately increases production of platelet-derived growth factor and monocyte chemoattractant protein-1 which, in turn, results in vascular smooth muscle cellular proliferation and inflammation [42, 43].

Finally, it should be noted that whereas oxonic acid-induced hyperuricemia resulted in increased oxidative stress and arterial pressure, uric acid administration may also have

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decreased oxidative stress and arterial pressure in experimental animals [44]. Thus, intra-peritoneal administration of uric acid for 5 weeks decreased arterial pressure and oxidative stress (as determined by a decreased malondialdehyde) in SHR (but not in WKY) [44].

In summary, the foregoing results obtained in animal models (mostly rat models) of hyperuricemia regarding the role of uric acid in the development of hypertension and renal injury have been inconclusive. In some models, an increased serum uric acid level was clearly a marker of hypertensive disease coinciding with deranged renal hemodynamics. In others, hyperuricemia appeared to be the main pathogenetic factor in the development of hypertension and renal derangements, associated with interstitial inflammation and fibrosis, glomerular hypertension, afferent arteriolar nephropathy, and glomerular hypertrophy. There are several possible reasons for this discrepancy. First, several rat substrains were used in those studies which may differ in susceptibility to the harmful effects of uric acid. For example, in Sprague-Dawley rats, hyperuricemia induced hypertension and renal injury, whereas in the SHR hyperuricemia was only a biomarker of renal hemodynamic changes. Second, some of the substances used in these experiments may have exerted their effect directly and not through their effect on uric acid levels. Thus, allopurinol (a xanthine oxidase inhibitor) that was used to lower uric acid levels has antioxidant properties, and its beneficial effect may be direct and not attributable to the serum uric acid reduction. Third, the mechanism of hyperuricemia was different in various models. Thus, in the SHR, hyperuricemia was a 'compensatory event' necessary to overcome primary impairment in urinary excretion of uric acid (due to renal hemodynamics changes). At the moment that hyperuricemia is established, the production and excretion of uric acid remain in equilibrium, and the excretion of uric acid is the same as in their normotensive counterparts. On the other hand, in experiments with oxonic acid, there was an increased production of uric acid and, consequently, these rats produced and excreted more uric acid than their control animals. In other words, the total uric acid load is far greater in oxonic acid-treated animals than in the other models. Similarly, one recent review forwarded the notion of different effects of serum uric acid concentration versus intracellular uric acid [45].

Clinical and Epidemiological Studies

Before discussing the evidence related to the association of hyperuricemia acid and various cardiovascular and renal disorders, we will mention the findings of Ferris and Gorden [46] who unequivocally demonstrated that serum concentration of uric acid depended upon renal hemodynamic alterations. That study was obtained in healthy human volunteers, and the subjects received infusions of either angiotensin II or norepinephrine in an amount sufficient to increase the diastolic pressure to 20 mm Hg above its baseline value. Glomerular filtration rate and renal blood flow were measured with inulin and paraaminohippurate, respectively. Measurements of relevant variables were made at baseline, during infusions of either vasoconstrictor, and after their recovery periods. Infusion of either pressor infusion increased arterial pressure and reduced glomerular filtration and effective renal blood flow associated with the ensuing hyperuricemia. Upon discontinuation of the infusion, the renal hemodynamic and serum uric acid concentration immediately returned to normal. These results clearly demonstrated that the serum uric acid level was dependent on renal hemodynamics [46]. Thereafter, several clinical reports from our investigative group further extended the finding of Ferris and Gorden [5, 47, 48]. Thus, Messerli et al. [5] demonstrated that, in patients with essential hypertension, the serum uric acid concentration was directly related to renovascular resistance and inversely related to renal blood flow. These findings clearly suggested that hyperuricemia in patients with essential hypertension was a consequence of

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renal hemodynamic derangements. Thereafter, we demonstrated that in patients with hypertensive vascular disease, the serum uric acid concentration was inversely related to the renal distribution of cardiac output [47]. Finally, Nunez et al. [48] reported that, in patients with renal arterial disease and hypertension, surgical correction of the occlusive arterial lesion significantly reduced serum uric acid concentration. Each of these findings provide compelling evidence that, in hypertensive disease, hyperuricemia was related to intrarenal hemodynamic disturbance and gave further credence to our concept that the serum uric acid concentration is a marker of renal hemodynamic dysfunction.

On the other hand, a number of studies have demonstrated a clear association of hyperuricemia with hypertension and chronic renal disease [5, 49–52]. Furthermore, several very detailed reviews indicated that increased serum uric acid predicted the risk of subsequent hypertension and kidney disease [5, 19, 53]. However, it should be noted that no causative relationship between hyperuricemia and hypertension has been established. Consequently, the statement that hyperuricemia predicts hypertension is as equally valid as the statement that hypertension predicts hyperuricemia. It is also worth noting that, once established, hyperuricemia may exert adverse vascular and renal effects and thus may contribute to the progression of cardiovascular and renal damage as a contributory but not causal factor. Moreover, there were very few clinical trials on the effects of lowering serum uric acid on hypertension and chronic kidney disease and the results of those studies have been inconclusive, at best [53]. Apparently, the only exception may be the impact of serum urate lowering in hyperuricemic adolescents with newly diagnosed essential hypertension. Therapy with either allopurinol (a xanthine oxidase inhibitor) or probenecid (a uricosuric agent) was shown to reduce both serum uric acid and arterial pressure [54, 55]. Thus, except for hypertensive adolescents, the conventional therapy for hypertensive patients and patients with renal disease has been recommended.

This short report was focused on the association between hyperuricemia and hypertensive cardiovascular disease. However, in addition to hypertension, a number of other cardiovascular, renal, and metabolic diseases were found to be associated with increased serum uric acid concentration. Thus, several studies published recently in *Cardiorenal Medicine* and elsewhere clearly indicated that hyperuricemia may be involved in the pathogenesis of cardiovascular and renal diseases, insulin resistance, and metabolic disorders [56–61]. Apparently, an increased serum uric acid level may contribute to increased oxidative stress, endothelial dysfunction, increased vascular stiffness, and inappropriate reaction of the renin-angiotensin system [56]. This, in turn, may adversely affect cardiovascular and renal function and structure, as well as associated metabolic events.

Conclusion

The results of many clinical and experimental studies clearly demonstrate that an increasing serum uric acid level may be a useful biomarker of hypertension and its consequently deranged renal hemodynamics. It is also evident that chronic hyperuricemia may adversely affect cardiovascular and renal structure and function and, therefore, may be a contributory event in the pathogenesis of cardiovascular and renal disorders. Thus, at present, there is no clear or convincing evidence that hyperuricemia is a causative factor in hypertensive disease or that lowering the uric acid concentration may reduce arterial pressure. Therefore, conventional pharmacotherapy, without uricosuric agents, is recommended in the treatment of hypertensive cardiovascular disease unless there is concern about tissue deposition of urate. One exception may be the population of obese hypertensive adolescents in whom reduction of hyperuricemia has been shown to result in a decreased arterial pressure.

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Disclosure Statement

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