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Unearthing uric acid: An ancient factor with recently found significance in renal and cardiovascular disease

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Uric acid is strongly associated with cardiovascular and renal disease, but is usually not considered to have a causal role. However, recent experimental, epidemiological, and clinical studies provocatively suggest that uric acid may contribute to the development of hypertension, metabolic syndrome, and kidney disease in some patients. Clinical studies are urgently needed to examine this important possibility.

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Following the discovery by Garrod in the early 1800s that hyperuricemia was the cause of gout, hyperuricemia was proposed to have a causal role in a variety of cardiovascular and renal conditions, including hypertension (Frederick Mahomed), arteriolosclerosis (Henri Huchard), kidney disease (Garrod and George Johnson), and heart disease (Peter Hood). This was not surprising, as natural history showed that 25–50% of gouty subjects had hypertension, 75% were obese, 25% died with kidney failure, and 90% developed cardiac disease, making gout the most important cardiovascular risk factor then known. By the mid-1900s, however, the causal nature of uric acid in these conditions was questioned, as it was recognized that the association of gout with cardiovascular disease might simply reflect that gout and cardiovascular complications have similar risk factors (obesity, kidney disease, etc). This was addressed in epidemiologic studies by asking whether uric acid was an independent risk factor for cardiovascular and renal disease, while controlling for other known risk factors such as hypertension and metabolic syndrome. Some studies continued to find uric acid an independent risk factor; however, others could not. The inconclusiveness of the data, the supposition that soluble uric acid was biologically inert or even an antioxidant, and the finding that the increase in uric acid might be secondary to either a decrease in glomerular filtration rate or the presence of hyperinsulinemia, all led to the conclusion that uric acid was likely not a true cardiovascular or renal risk factor.[1] Consequently, the uric acid measurement was removed from the routine blood panel, recommendations were made not to measure it routinely in patients with cardiovascular or renal disease, and it was deleted as a risk factor from the list provided by most cardiovascular and renal societies. A 'requiem' for uric acid as a renal risk factor was celebrated in this very journal,[2] and uric acid was laid to rest.

An 'unearthing' of uric acid as a cardiovascular and renal risk factor occurred in the late 1990s when it was recognized that there were certain assumptions that had been made with

the various analyses.[3,4] For example, uric acid need not be an independent risk factor for cardiovascular disease in order to be a causal risk factor. Thus, if uric acid caused hypertension or kidney disease, it would not necessarily be independent of these factors as a cardiovascular risk factor (similar to the fact that hypertension is not independent of left ventricular hypertrophy as a risk for cardiac death).[4] Similarly, the finding that a decreased glomerular filtration rate caused urate retention did not rule out the possibility that the rise in uric acid might contribute to the subsequent renal decline.[3] Perhaps, most importantly, the conclusions that uric acid was not important had never been tested by direct experimental studies in animals or cell culture.[3,4]

Recent studies have raised the exciting possibility that uric acid may indeed have a contributory causal role in cardiovascular and renal disease. A brief summary of the current state of knowledge is presented. Due to the nature of the review, only select references are provided.

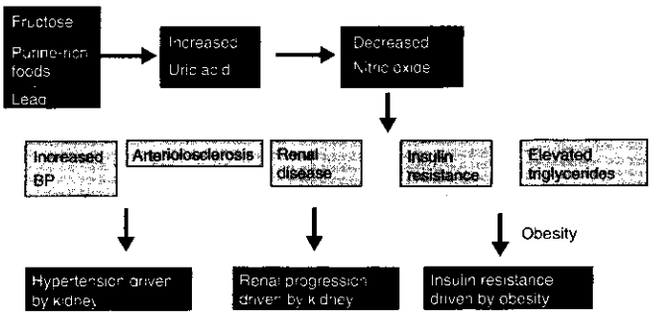

Figure 1 | Uric acid as a potential initiator of the cardiovascular and renal disease epidemic. According to the model, an elevated uric acid induced by diet (fructose, purines, or lead exposure) may have a role in initiating hypertension, arteriolosclerosis, kidney disease, insulin resistance, and hypertriglyceridemia. However, once renal microvascular disease develops, the kidney will also drive the hypertension; once obesity occurs, the fat-laden adipocytes will promote continued insulin resistance, and one kidney disease is manifest, the kidney will also drive progression. Uric acid may thus be viewed as both an initiator and accomplice in driving the epidemic.

STUDIES OF THE *IN VITRO* EFFECTS OF URIC ACID

Soluble uric acid is not inert after all, but has been found to have many biological properties. A major beneficial property is its ability to act as an aqueous antioxidant. Some studies suggest that, along with ascorbate, urate may be one of the most important antioxidants in plasma. Uric acid will react with a variety of oxidants, particularly peroxynitrite, and will undergo subsequent oxidation through a series of reactions resulting in the formation of allantoin. The ability of urate to react with oxidants has been shown to have a beneficial role on vascular cells in tissue culture under some conditions associated with oxidative stress,[5] and this has led to the notion that a rise in uric acid in cardiovascular disease might represent a compensatory attempt of the host in response to the oxidative stress known to occur.[6]

In contrast, soluble uric acid has also been found to have a wide variety of deleterious effects on vascular cells. Uric acid has been found to enter vascular smooth muscle cells, via specific organic anion transporters and activate intracellular mitogen-activated protein kinases (such as p38 and extracellular signal regulated protein kinase), and nuclear transcription factors (nuclear factor-kappa B and activator protein-1), resulting in a proliferative and proinflammatory phenotype: vascular smooth muscle cells produce growth factors (platelet-derived growth factor), vasoconstrictive substances (cyclooxygenase-2 induced thromboxane and angiotensin II), proinflammatory molecules (C-reactive protein and monocyte chemoattractant protein), and the type I angiotensin II receptor[7–10] (unpublished data). Uric acid also has profound effects on endothelial cells, resulting in an inhibition of proliferation and migration, the stimulation of C-reactive protein, and the inhibition of nitric oxide release.[10,11]

The mechanism by which urate activates vascular cells is being actively studied in our laboratory. One potential mechanism relates to the discovery that the reaction of uric acid with oxidants results in the release of a variety of degradation products that are biologically free radicals.[12] It is interesting that antioxidants can block the effect of uric acid on vascular smooth muscle cells.[8] Currently, we are trying to identify these radicals and determine if they are being produced *in vivo*.

Studies in experimental models of hyperuricemia have also provided major insights into potential pathogenic roles of uric acid in renal and cardiovascular disease. These are summarized below (Figure 1), along with recent clinical studies.

DISEASES IN WHICH URIC ACID MAY HAVE A CONTRIBUTORY ROLE

Essential hypertension and arteriolosclerosis

An exciting observation was the finding that experimental hyperuricemia in rats results in the development of hypertension. This occurs in two steps, with the first phase driven by a fall in nitric oxide and an activation of the renin angiotensin system, and with the second phase driven by uric acid mediated renal microvascular disease.[7,13] The renal microvascular disease was shown to occur independently of hypertension and clinically resembled the renal arteriolosclerosis lesion of human hypertension.[14] Consistent with this finding have been a large number of epidemiological studies reporting that an elevated uric acid is an independent predictor of hypertension (reviewed in Johnson *et al.*[15]). In all studies reported, uric acid has been an independent risk factor, and in all studies the relationship of uric acid with blood pressure has been dose-dependent, linear, and consistent.[15] Studies of new onset essential hypertension in adolescents have reported an elevation of uric acid (>5.5 mg/dl) in 90% of hypertensive subjects versus 0% of controls, and the relationship of uric acid with hypertension was linear and dramatic ($r=0.8$).[16] In preliminary studies, the lowering of uric acid resulted in the normalization of blood pressure in four of five hypertensive adolescents.[17]

Currently, there are two NIH trials ongoing to determine the effect of lowering uric acid in the hypertensive adolescent, and in the African American receiving diuretics for stage I hypertension.

Metabolic syndrome

An interesting observation relates to the finding that the ingestion of fructose, present in various sweeteners and sugar, is strongly associated with the development of the metabolic syndrome and the ongoing obesity epidemic.[18] Fructose is the only sugar that causes a rise in uric acid, and it does so rapidly following ingestion. We hypothesized that the rise in uric acid could have a role in the development of insulin resistance through a urate-induced inhibition of endothelial nitric oxide. A decrease in endothelial nitric oxide bioavailability would counter the effects of insulin, which acts in part by stimulating blood flow to skeletal muscle via nitric oxide.[19] Subsequently, we found that lowering uric acid prevented or improved most features of the metabolic syndrome in fructose-fed rats, including the prevention of hyperinsulinemia, hypertriglyceridemia, hypertension, and weight gain.[20] Studies in humans have also found that uric acid is a potent predictor of both hyperinsulinemia[19] and weight gain,[21] and an elevated uric acid is observed in the vast majority of subjects with metabolic syndrome. Clinical studies are now being planned to determine if lowering uric acid may be able to prevent the development of this important medical problem.

Chronic kidney disease

Experimental studies demonstrated that hyperuricemia caused the slow development of kidney disease, with the development of albuminuria, microvascular disease, glomerulosclerosis, and tubulointerstitial fibrosis.[22] Hyperuricemia was also found to accelerate renal disease of other etiologies, particularly the remnant kidney model.[9] A variety of mechanisms were identified, including the stimulation of intrarenal renin expression with renal hypertrophy, glomerular hypertrophy, acceleration of intrarenal microvascular disease, and the development of glomerular hypertension and renal vasoconstriction.[9,22,23] Micropuncture studies demonstrated that the development of glomerular hypertension was largely due to the induction of preglomerular vascular disease that altered renal autoregulation.[23] Recent clinical studies have also confirmed that uric acid is a major independent risk factor for the development of renal disease both in the normal population and in subjects with kidney disease due to immunoglobulin A nephropathy. In one study of the general population, hyperuricemia carried a greater risk than proteinuria for the subsequent development of renal insufficiency.[24] Recently, a prospective controlled trial examined the effect of lowering uric acid in patients with chronic kidney disease and hyperuricemia.[25] Subjects in whom uric acid was lowered (from 9.75 to 5.8 mg/dl) showed less renal progression (16%) versus controls (46%) over the 1-year follow-up, and this was associated with an 11 mm Hg fall in systolic blood pressure in the treated group versus no change in systolic blood pressure in the control group.[25] While these observations are exciting, additional confirmation is needed.

Transplant-associated kidney disease

Hyperuricemia is common in transplant patients and is a side effect of calcineurin inhibition. Interestingly, several experimental studies suggest that hyperuricemia mimics and exacerbates cyclosporine nephropathy,[26] whereas lowering uric acid may have a renoprotective role.[27] Recently, the lowering of uric acid in liver transplant subjects was reported to improve renal function.[28] It is also of interesting that the induction of experimental hyperuricemia, particularly in the remnant kidney model, is histologically identical to chronic allograft nephropathy.[9] This raises the interesting hypothesis that hyperuricemia may be an important antigen-independent risk factor for this condition, which is the major cause of late allograft loss. Indeed, new onset gout in the renal transplant patient has recently been found to be an independent risk factor for both death and graft loss.[29]

Other renal and cardiovascular syndromes

Several studies also suggest that uric acid may have a contributory role in pre-eclampsia,[30] in intrauterine growth retardation and a congenital reduction in nephron number,[17] in endothelial dysfunction,[31] and in inflammation.[8–10] Unpublished studies in our laboratory also suggest it may have a contributory role in acute renal failure, possibly through its vasoconstrictive and proinflammatory effects.

CONCLUSION

It is evident that more studies on the role of uric acid in cardiovascular and renal disease are required. In particular, identifying the conditions under which uric acid may be beneficial versus deleterious are critical. Whether uric acid represents 'King Priam's treasure' and is at the core of the cardiovascular and renal epidemic is an exciting possibility but remains to be proven. Regardless, it is clear that the unearthing of this ancient factor will provide new insights into cardiovascular and renal biology.

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