SERUM URIC ACID: AN INDEPENDENT RISK FACTOR FOR VASCULAR INJURY

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BACKGROUND

Hyperuricemia (serum uric acid levels >8mg/dl) has been associated with hypertension for a long time.1 At some point it was felt that elevated uric acid levels were the result of decreased kidney function, but recent clinical and experimental data have shown a direct correlation between high uric acid levels and progression of vascular injury, leading to increased cardiovascular morbidity and mortality, hypertension, and accelerated loss of kidney function.[2] The mechanism of action appears to be mediated by the profound effects of uric acid in human vascular cells, which include endothelial dysfunction, vascular proliferation, and nitric oxide release from vascular cells.3•5 Moreover, as a consequence of afferent arteriolar injury by hyperuricemia, chronic tubulointerstitial changes leading to progressive loss of kidney function and worsening hypertension can occur.[6]

Strategies to treat asymptomatic hyperuricemia should be considered in high-risk individuals to prevent progression of cardiovascular disease and chronic kidney disease.

THE KIDNEY AND URIC ACID HANDLING

Hyperuricemia is a common clinical finding that has been correlated co several medical conditions. The most common is gout, which is known co affect at least five million Americans and is frequently associated with impaired kidney funcrion.[7] Elevated uric acid levels are important markers of eclampsia and have also been associated with essential hypertension, atherosclerotic cardiovascular disease, and the "Metabolic Syndrome" that is characterized by obesity, hyperinsulinemia, insulin resistance, type II diabetes mellitus, and hyperlipidemia.

The majori$_{ty}$ of hyperuricemia cases are due to impaired kidney handling of uric acid. The normal uric acid handling by the kidney is summarized in Figure 1.[8]

The question of whether hyperuricemia and its relationship to cardiovascular events is circumstantial versus causal has always been a matter of debate. Before the introduction of diuretics, hypertension had been associated with hyperuricemia. However, it's been shown chat the use of diuretics to treat elevated blood pressure can lead co hyperuricemia, further contributing co vascular injury. Despite JNC 7 recommendations about che use of diuretics as che treatment of choice for essential hypertension, we believe chat a small dose of hydrochlorothiazide (not co exceed 12.5 mg/day) should only be prescribed for edematous patients in whom better choices of medications with additional systemic advantages - such as angiotensin-convercing enzyme inhibitors, angiotensin receptor block-

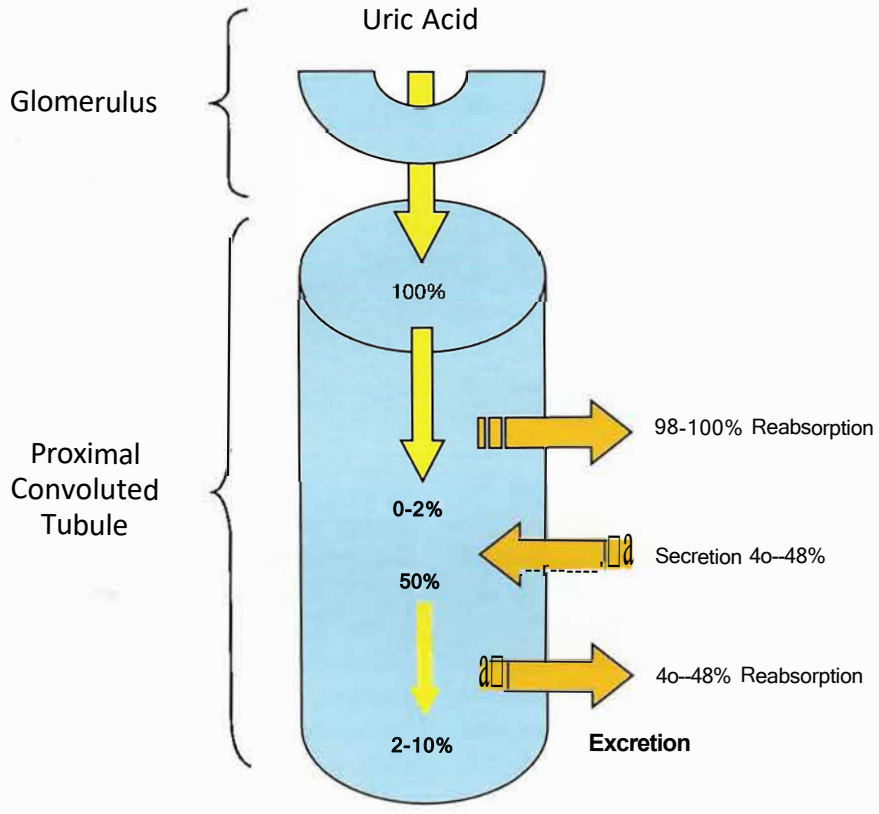

Figure 1. Normal uric acid handling by the kidneys.

ers, beca blockers, and calcium channel blockers- have failed co actain adequate blood pressure control. In addicion to elevated uric acid levels, diurecics can predispose one co arrhythmia induced by hypokalemia and hypomagnesemia. Moreover, diuretics stimulate the renin angiotensin system by inducing volume depletion and chrough the direct effects of hyperuricemia.9 Other drugs that can alcer uric acid levels are listed in Table 1.

There is evidence chat hyperuricemia in essential hypertension is an indicator of early renal vascular involvement, specifically arteriolar-nephrosclerosis.[10] The arteriolopathy caused by hyperuricemia at the afferent arteriolar level results in glomerular hypertension, which leads to renal hypoperfusion and ischemia with the ensuing tubulointerstitial inflammation and fibrosis as well as worsening hypertension.2 Since the kidneys are highly vascular organs, che finding of microalbuminuria in a random urine specimen has been accepted as a marker of renal vascular injury and systemic vascular disease, for which chis simple test has become a useful di$_{ag}$nostic tool.

While hyperuricemia could be the consequence of impaired uric acid excrecion in some instances of incrinsic kidney disease, there is ample evidence co support che face chat elevated serum uric acid levels appear to have a pachogenie link with systemic vascular injury.[11] In face, the use of allopurinol, a xanthine oxidase inhibitor char reduces uric acid, has been shown to slow down che progression of kidney disease to frank Stage V CKD (end-stage kidney failure).[12]

The accive form of vitamin D (known as Hormone D - 1.25(0H)2D) plays an important role not only in maintaining mineral metabolism homeostasis (calcium x phosphorus produce, parathyroid hormone secretion) but also in a wider biologic range of functions, including cellular differentiation, immunoregulacory properties, and proper myocardial and skeletal muscle function. Uric acid suppresses 1 alpha-hydroxylase activity and synthesis of 1,25(0H)2D. This undesirable complication of hyperuricemia can be blocked by allopurinol.[13]

Uric acid levels as a risk factor for coronary heart disease and all-cause mortality, particularly among middle age men, has been reported in previous publications.[14, 15] However, other than for decreasing progression of arteriolar-nephrosclerosis with allopurinol, the issue of reversing coronary artery disease by correcting hyperuricemia needs more controlled long-term scudies.[16] There are currently prospective randomized controlled trials being conducted to differentiate whether the beneficial effect of allopurinol is mostly related co its xanchine oxidase inhibition, as opposed to the uric acid lowering effect, since reducing uric acid alone by probenecid may not have the same protective effect as allopurinol. Nevertheless, based on experience accumulated with regard co uric acid and vascular injury, it would appear as if measuring serum uric acid levels should be considered routine during metabolic profile testing.

The creatmenc of choice for hyperuricemia includes discontinuation {when possible) of potentially offending agents such as diuretics, notably metolazone. However, many patients still will require specific therapy with allopurinol. Intolerance to allopurinol, which can range from liver dysfunction to skin rash -particularly if concomitantly raking ampicillin[17] - to oftentimes fatal toxic epidermonecrolysis (TEN), can become a limiting factor in terms of its use. A new non-purine selective inhibitor of xanthine oxidase (Febuxostat) has been introduced as an alternative co allopurinol for the treatment of hyperuricemia and gout.[18] Likewise, for the treatment of acute hyperuricemia due to tumor lysis syndrome, intravenous rasburicase (Elitek) has been added to the cherapeutic armamentarium, although its use is mostly limited to the field of oncology. In a recent study, the use of acorvastatin significantly reduced serum uric acid levels, thus offsetting chis risk factor among individuals with coronary artery disease.[19] In general, the use of uricosuric agents to correct hyperuricemia should be discouraged since th$_{ey}$ can lead to renal interstitial damage.

Of interest is the fact chat during acute illness, hyperuricemia carries a very poor prognosis. Ir is felt that during an acute catastrophic event, tissue hypoxia contributes to the depletion of adenosine triphosphate (ATP) and activates purine nucleotide degradation to uric acid, usually predicting a poor outcome.[20]

Drugs Affecting Uric Acid Levels

Increased Uric Acid	Decreased Uric Acid
Diuretics	Allopurinol
Pyrazinamide	Febuxostat
Salicylate (low dose)	Probenecid
Cyclosporine	Sulfinpyrazone
Tacrolimus	Fenofibrate
Ethambutol	Losartan
Beta Blockers	Amlodipine

Table 1. Drugs that alter uric acid levels.

CONCLUSIONS

Since the kidneys are highly vascular organs, early signs of renal injury (microalbuminuria) have been accepted as markers of systemic cardiovascular injury. Elevated uric acid levels have been associated with vascular damage resulcing from endothelial dysfunction, cell proliferation/migration, and nitric oxide release leading co hypertension. Clinical studies showing decreased progression of chronic kidney disease imo Stage V CKD (end stage renal failure) by correction of hyperuricemia further lends credence to the relationship between uric acid levels and progressive vasculopachy. Likewise, hyperuricemia appears to be an independent risk factor for coronary artery disease, particularly when complicating the "Metabolic Syndrome." Uric acid and microalbuminuria levels are inexpensive and easy tests co perform and should be added to the routine metabolic profile. In high-risk individuals with coronary artery disease and chronic kidney disease (a frequent combination) who present with asymptomatic hyperuricemia (serum uric acid >8mg/dL), initiation of therapy with allopurinol seems co be warranred.21

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