The Role of Uric Acid in the Development in Progressive Renal Disease and Renal Fibrosis

Nelson P. Kopyt, M.D.

Department of Medicine, Temple University, USA

An elevation in circulating serum uric acid is strongly associated with the development of hypertension and renal disease, but it remains controversial whether uric acid (UA) has a causal role or whether it simply indicates patients at risk for these complications. We tested the hypothesis that UA may have a causal role in the development of hypertension and renal disease by examining the effects of mild hyperuricemia in rats. Mild hyperuricemia was induced in rats by providing a uricase inhibitor (oxonic acid) in the diet. Hyperuricemic rats developed elevated blood pressure after 3 weeks whilst control rats remained normotensive. The development of hypertension was prevented by concurrent treatment with either a xanthine oxidase inhibitor (allopurinol) or a uricosuric agent (benziodarone) both of which lowered uric acid levels. Perhaps more important is following the establishment of hypertension, blood pressure could also be lowered by reducing uric acid levels with either allopurinol or by oxonic acid withdrawal. A direct relationship was found between blood pressure and uric acid (r=0.75, n=69), with a 10 mmHg blood pressure increase for each 0.03 mmol/L (0.5 mg/dL) incremental rise in serum uric acid. The kidneys were devoid of urate crystals and were normal by light microscopy. However, immunohistochemical stains documented an ischemic-type of injury with collagen deposition, macrophage infiltration and an increase in tubular expression of osteopontin. Hyperuricemic rats also exhibited an increase in juxtaglomerular renin and a decrease in macula densa neuronal nitric oxide synthase. Both the renal injury and hypertension were reduced by treatment with enalapril or L-arginine. We further explored the role of UA in renal fibrosis in a model of cyclosporin induced nephropathy. In this model mild elevations in UA markedly increased fibrosis.

In conclusion, mild hyperuricemia causes hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal nitric oxide synthase.