SEMINARS IN
NEPHROLOGY

Hemodynamics of Hyperuricemia

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Prolonged hyperuricemia is associated with the development of hypertension, renal arteriolosclerosis, glomerulosclerosis, and tubulointerstitial injury. It confers a greater risk than proteinuria for developing chronic renal disease and is associated with the development of hypertension. Mild chronic hyperuricemia without intrarenal crystal deposition was induced in rats by inhibiting uricase with oxonic acid. Hyperuricemic rats developed hypertension, afferent arteriolar thickening, and mild renal interstitial fibrosis. Additionally, hyperuricemia accelerated renal damage and vascular disease in rats undergoing renal ablation. To better understand the role of hyperuricemia in the kidney, micropuncture studies were performed. Hyperuricemia resulted in renal cortical vasoconstriction (single nephron glomerular filtration rate (SNGFR) ↓ 35%, $P < .05$) and glomerular hypertension ($P < .05$). The possibility that hyperuricemia could modify renal hemodynamic disturbances during progression of renal disease was tested in rats with 5/6 nephrectomy. Hyperuricemia accentuated the renal vascular damage and caused cortical vasoconstriction (SNGFR ↓ 40%, $P < .05$) and persistent glomerular hypertension. In conclusion, hyperuricemia impairs the autoregulatory response of preglomerular vessels, resulting in glomerular hypertension. Lumen obliteration induced by vascular wall thickening results in severe vasoconstriction. The resulting ischemia is a potent stimulus that induces tubulointerstitial inflammation and fibrosis as well as arterial hypertension.
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It is well established that prolonged hyperuricemia, such as observed in gouty patients, is associated with chronic renal disease. Renal histologic changes including arteriolosclerosis, glomerulosclerosis, and tubulointerstitial injury are present in up to 75% to 99% of patients with gout;[1] in addition, decreased glomerular filtration rate (GFR) has been reported in 30% to 60% of the cases. Early studies by Yu et al[2] evaluated renal function in gouty patients. Renal hemodynamics as measured by inulin clearance and para-aminohippurate clearance were evaluated in 149 patients with primary gout over intervals of 2 to 22 years and 111 patients were followed-up for up to 5 years. Two thirds of patients had renal dysfunction associated with hypertension or with an age older than 50 years. Because renal function was normal in the remaining patients who had gout in the absence of other risk factors, it was concluded that gout did not produce direct injury to the kidney. However, excluding patients because of hypertension is probably not valid because essential hypertension does not invariably result in renal failure and the possibility that hyperuricemia could induce hypertension was not considered. Thus, despite the conclusion reached by the investigators, this study shows that gout is associated with renal impairment in many patients.

Evidence that uric acid may cause renal damage is suggested by studies of the rare condition of familial juvenile hyperuricemic nephropathy (FJHN). This entity was first described in 1960 in a family with gout, hyperuricemia, and renal disease.[3] However, gout is not invariably present and in contrast to primary gout, FJHN affects young men, women, and children. In addition, interstitial deposits of urate are uncommon in renal biopsy specimens.[3] The hallmark of this disease is dominantly inherited hyperuricemia resulting from a drastically decreased fractional excretion of urate (FE_{urate}).[4,5] Studies in children of these families showed that hyperuricemia plus decreased FE_{urate} is found in 50% of apparently healthy siblings and precedes the deterioration in renal function, consistent with a causative role for uric acid in this

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nephropathy.[4] Supporting this contention, several studies have reported that early treatment of FJHN with allopurinol, when renal function still is normal or mildly decreased, resulted in continued stable renal function or even slight improvement for a decade or more.[6,7] In contrast, treatment started after renal damage has occurred almost always is associated with rapid progression to dialysis and transplantation[6,8,9]

Additional evidence that uric acid may cause renal impairment is provided by a recent study in liver transplant patients. In this study, serum creatinine levels were higher in hyperuricemic than in nonhyperuricemic patients and the peak uric acid level correlated with the corresponding serum creatinine level ($r = 0.7$). Importantly, treatment with allopurinol for 3 months resulted in a decrease in the serum creatinine level ($P = .01$) in the absence of changes in the type or dose of immunosuppression.[10] These studies confirm that increased uric acid levels are associated with an impairment of renal function in many cases.

Hyperuricemia also has been related to hypertension and vascular damage. In 1966, Cannon et al[1] reported that renal urate clearance was inappropriately low in proportion to GFR in 14 of 17 patients with untreated essential hypertension and suggested that hyperuricemia may induce or accelerate kidney damage associated with hypertensive vascular disease. More recently, Messerli et al[11] evaluated the effect of hyperuricemia on renal hemodynamics in normotensive subjects and patients with uncomplicated essential hypertension. They found that mild asymptomatic hyperuricemia was associated with diminished renal blood flow and increased renal vascular resistance regardless of the level of arterial pressure and GFR. They suggested that the unexplained high frequency of hyperuricemia in the essential hypertensive population most likely reflects hypertensive vascular disease and early nephrosclerosis. As in humans, some models of experimental hypertension are associated with increased levels of serum uric acid.[12,13] Serum uric acid is increased in the spontaneously hypertensive rats treated with deoxycorticosterone acetate salt (DOCA-salt); the increase correlates with the markedly decreased renal blood flow and increase in vascular resistance index compared with control spontaneously hypertensive rats. Histologic examination of the kidneys of DOCA-salt –treated spontaneously hypertensive rats revealed extensive vascular wall thickening and obstruction of small arteries with fibrinoid necrosis in all studied rats. Findings in both human and experimental studies lead these investigators to suggest that decreased renal blood flow and hyperuricemia may share a common mechanism; however, none was proposed.[13]

Other clinical studies also support the association of hyperuricemia and renal vasoconstriction. Mattei et al[14] evaluated renal hemodynamics in untreated microalbuminuric and normoalbuminuric patients with essential hypertension. They found that the microalbuminuric patients had significantly higher systolic blood pressures and higher renal vascular resistances. In addition, there was a significant positive correlation between urinary albumin excretion and serum uric acid level. These observations are consistent with the association of hyperuricemia and renal vasoconstriction in microalbuminuric essential hypertensive patients. However, in these studies, the question of whether hyperuricemia is the result or the cause of renal dysfunction remained unsolved.

Controversy arose because previous models of hyperuricemia resulted in a marked increase of serum uric acid level and uricosuria that produced intratubular crystal deposition, acute renal failure, and premature death.[15,16] Undoubtedly, these models of severe hyperuricemia were useful for studying acute urate nephropathy, however, they were not appropriate to explore the effects of the mild hyperuricemia that is observed in conditions such as FJHN, hypertension, or gout.

Effects of Hyperuricemia on Glomerular Hemodynamics

Recently, an experimental model of mild chronic hyperuricemia was developed in rats receiving a low-sodium diet. Inhibition of uricase with oxonic acid (OA) induced an up to 3-fold increase in serum uric acid level without intrarenal crystal deposition.[17] Rats developed hypertension, afferent arteriolar thickening, and mild renal interstitial fibrosis, with interstitial collagen deposition and macrophage infiltration. These effects could be prevented if serum uric acid (SUA) levels were maintained in the normal range with either xanthine oxidase inhibitors or uricosuric agents.[17,18]

The use of micropuncture techniques in these rats allowed us to characterize the renal and glomerular hemodynamic changes associated with mild hyperuricemia and to correlate them with structural injury.[19] A low-salt diet containing 2% oxonic acid was administered to rats for 5 weeks, at which time micropuncture studies were performed. To distinguish the effects of hyperuricemia from those of OA, a group of rats received allopurinol, an inhibitor of xanthine oxidase, to prevent the increase in uric acid induced by OA. Mild hyperuricemia was observed in association with development of modest hypertension noted by intra-arterial and tail-cuff measurements. The increase in SUA level and the increase in blood pressure were prevented by allopurinol; a significant positive linear regression between SUA levels and systolic blood pressure was found.[19]

Micropuncture studies in rats receiving OA showed that hyperuricemia was associated with a significant increase in glomerular capillary pressure (P_{GC}) to 56.7 ± 1.2 mm Hg, a value significantly greater than that observed in rats on a low-salt diet (51.9 ± 1.4 mm Hg, $P < .05$). Allopurinol treatment in rats on OA prevented the increase in glomerular pressure (50.1 ± 0.8 mm Hg, $P < .01$ versus OA) (Fig 1). A significant positive linear regression was observed between SUA level and P_{GC}. Glomerular pressure also correlated with SBP and mean arterial pressure (MAP).[19]

In these studies, a low-salt diet was associated with cortical vasoconstriction (as has been described previously) and values of glomerular plasma flow and SNGFR were lower than normal and were not different from those values in hyperuricemic rats. Afferent and efferent resistances tended to be higher in OA–treated rats but differences were not statisti-

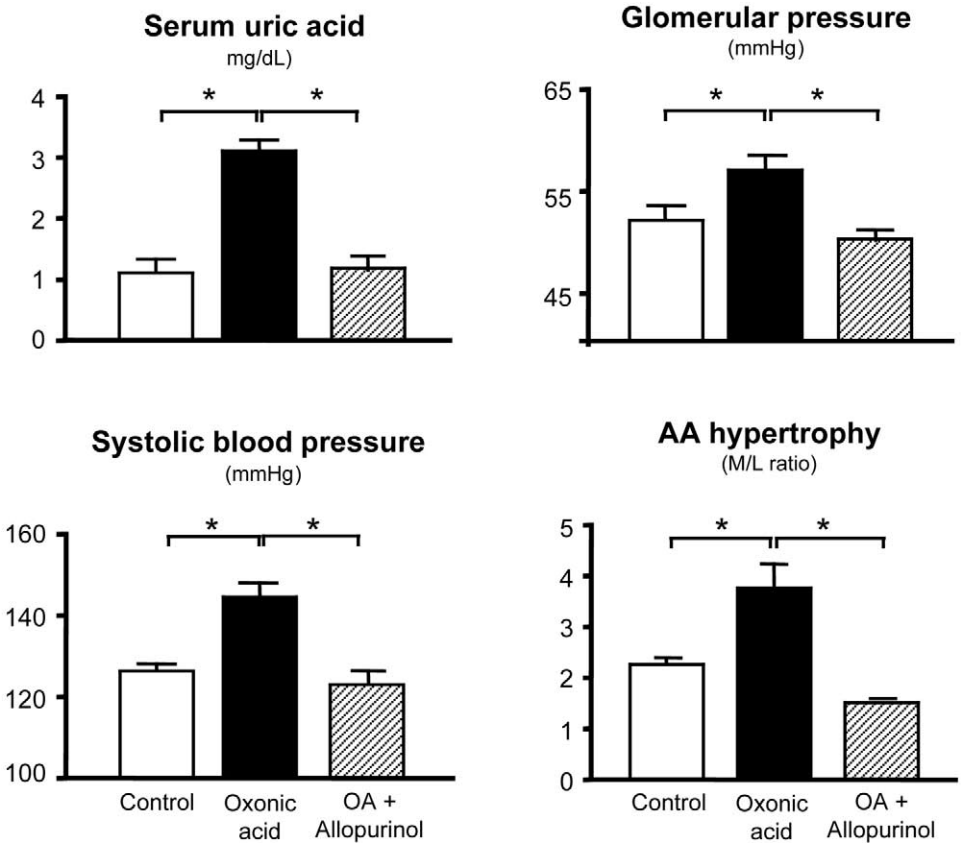

Figure 1 Oxonic acid induced hyperuricemia in normal rats on low-salt diet producing systemic and glomerular hypertension associated with afferent arteriole hypertrophy. Concomitant treatment with allopurinol prevented these alterations. *$P < .05$.

cally significant; however, there was a significant positive correlation between MAP and afferent resistance ($r^2 = .33$, $P < .003$). Importantly, the normal vasoconstrictive response of preglomerular vessels to increased mean arterial pressure in hyperuricemic rats was insufficient to prevent increased transmission of systemic pressure to the glomerular capillaries, as indicated by the increase in P_{GC}.[19]

To further evaluate the impact of hyperuricemia on glomerular hemodynamics without the effects of a low-salt diet we recently studied rats on a normal salt diet. Administration of OA by gavage for 5 weeks increased SUA acid level by 2-fold (2.5 ± 0.15 to 5.4 ± 0.23 mg/dL, $P < .01$). In a group receiving OA and allopurinol the increase in SUA level was prevented (2.6 ± 0.2 mg/dL). The increase in SUA level was associated with a modest increment in both systolic and mean arterial pressure. However, in contrast to rats studied on a low-salt diet, the vasoconstrictive effect of hyperuricemia clearly was shown. Whole-kidney GFR was decreased by 13% and was restored to normal by allopurinol. Glomerular hemodynamic studies showed marked cortical vasoconstriction as indicated by a significant increase of afferent and efferent resistances, as well as by a 35% decrease of single-nephron GFR (SNGFR) caused by the simultaneous decrease of glomerular plasma flow and the ultrafiltration coefficient. Despite renal cortical vasoconstriction, glomerular capillary pressure was increased significantly. These changes were prevented by allopurinol. Individual SUA values correlated positively with afferent and efferent resistances and negatively with the ultrafiltration coefficient and SNGFR.

On histologic examination there were no significant changes in glomerular or tubulointerstitial structures by routine light microscopy; however, immunostaining for α-smooth muscle actin showed hypertrophy of preglomerular vessels in hyperuricemic rats. Arteriolar thickening was prevented completely by allopurinol treatment ($P < .01$) (Fig 1). A significant positive correlation was found between arteriolar hypertrophy (measured as arteriolar area) and systolic blood pressure (SBP), serum uric acid, and P_{GC}.

The main finding in these studies was that hyperuricemia in the OA model is associated with renal cortical vasoconstriction and glomerular hypertension. A striking correlation between SUA level and total vascular resistance and glomerular hydrostatic pressure was observed within individual rats. Evidence that this effect was caused by uric acid, and not OA, was provided by including groups that received allopurinol. These groups maintained normal uric acid levels despite receiving OA, and showed no increase in vascular resistance and P_{GC}.[19]

The normal response to an increase in mean arterial pressure is afferent arteriolar vasoconstriction, which is an autoregulatory mechanism that acts to prevent the transmission of the increased pressure to the glomerular circulation. In hyperuricemic rats, the increase in afferent resistance was insufficient to prevent transmission of increased pressure to the glomeruli; this probably is related to the afferent arteriolopathy that occurs in this model.[18] This arteriolopathy was characterized by increased arteriolar thickness and media-to-lumen ratio with increased α-smooth muscle actin staining.

It has been reported previously that arteriolopathy develops independently of blood pressure, although it is dependent on the renin-angiotensin system.[18] It also may be mediated by direct effects of uric acid on vascular smooth muscle cells.[18,20] Interestingly, there was a significant correlation between arteriolar thickening and glomerular pressure.[19] One may speculate that arteriolar disease may have contributed to the transmission of SBP into the glomeruli because proliferation of vascular smooth muscle cells and increased collagen deposition in the vascular wall might be expected to increase rigidity of the vascular wall and thus limit its capacity to contract in response to higher perfusion pressure.

Increased glomerular pressure is known to precede (and is thought to be partially responsible) for the late development of hypertrophy and sclerosis in other experimental models (eg, subtotal renal ablation). P_{GC} was slightly lower in our hyperuricemic rats than in rats 4 to 6 weeks after 5/6 nephrectomy: 56.7 versus 60 mm Hg.[21-24] However, the increase of P_{GC} in hyperuricemic rats probably reflects a more significant dysfunction of preglomerular vessels because after renal ablation, blood pressure is higher (170-190 mm Hg), renal mass is decreased, and there is a significant degree of afferent dysfunction; in contrast, in hyperuricemic rats, hypertension is less severe and the nephron population remains intact.

Effects of Hyperuricemia in the Progression of Renal Injury

Hyperuricemia has long been associated with renal disease; it is an independent risk factor for progression in immunoglobulin A nephropathy[25,26] and confers a greater risk than proteinuria for developing chronic renal disease in the general population.[27] In experimental studies, mild hyperuricemia produces hypertension, renal vasoconstriction, tubulointerstitial injury, and arteriolopathy in normal animals. It also exacerbates cyclosporine nephrotoxicity.[17,18,28] Despite these associations, controversy exists as to whether uric acid has a causative role. Recently, the possibility that hyperuricemia could be contributing to progression of renal damage was tested by Kang et al[29] in the remnant kidney model. Mild hyperuricemia was induced by administering a normal sodium diet containing 2% OA. Rats developed hyperuricemia and showed higher blood pressure, greater proteinuria, and higher serum creatinine than control rats. Hyperuricemic remnant kidney rats also showed greater glomerulosclerosis, interstitial fibrosis, and vascular disease consisting of thickening of the preglomerular arteries with smooth muscle cell proliferation. Allopurinol significantly decreased uric acid levels and blocked the renal functional and histologic changes. Benziodarone decreased uric acid levels less effectively and only partially improved blood pressure and renal function, with minimal effect on the vascular changes.

Studies for determining the mechanism of the development of the vascular disease showed that uric acid directly stimulates vascular smooth muscle cell proliferation. In this study Kang et al[29] found de novo expression of cyclooxygenase-2 messenger RNA after incubation of vascular smooth muscle cells with uric acid. A cyclooxygenase-2 inhibitor or a TXA-2 receptor inhibitor prevented the proliferation in response to uric acid. In vivo, cyclooxygenase-2 also was shown to be expressed de novo in the preglomerular vessels and its expression correlated both with the uric acid levels and with the degree of smooth muscle cell proliferation. These studies provided direct evidence that uric acid may be a true mediator of renal disease and progression.

In experimental animals, a decrease of the renal mass results in glomerular hypertension and hyperfiltration of the remnant nephrons that cause proteinuria, glomerulosclerosis, and tubulointerstitial inflammation and fibrosis. The increase in P_{GC} results from ineffective constriction of the afferent arteriole that allows the transmission of the systemic hypertension to the glomerular tuft.[21-24] Thus, glomerular hemodynamic changes are determined to a great extent by the functional capacity of preglomerular arterioles. Recently, we reported that arteriolopathy of afferent arteriole may contribute to the progression of renal disease by perpetuating glomerular hemodynamic stress.[24] In renal ablated rats, histologic examination and morphometry showed thickening of afferent arterioles as disclosed by a significant increase in the media/lumen ratio, indicating hypertrophy of the vessel wall. Proliferation of vascular smooth muscle cells and increased collagen deposition might be expected to increase the rigidity of the vascular wall and thus limit its capacity to contract in response to higher perfusion pressure.[24] Maneuvers that prevent the accompanying inflammatory process, such as treatment with the heparinoid pentosan polysulfate[23] and the immunosuppressive drug mofetil mycophenolate,[24] preserve arteriolar structure and maintain normal glomerular pressure despite persisting systemic hypertension, indicating a normal autoregulatory response.

On the other hand, hypertrophy of vascular smooth muscle cells and expanded extracellular matrix on the vascular wall may critically decrease the lumen of preglomerular vessels, inducing the decrease of blood flow to glomeruli and postglomerular ischemia, which is a well-known stimulus to produce tubulointerstitial fibrosis and salt-sensitive hypertension.[30]

Because hyperuricemia accelerates progression of renal disease in the remnant kidney model by a mechanism intricately linked to the development of severe preglomerular vascular disease,[29] we performed micropuncture studies to evaluate the contribution of glomerular hemodynamic changes.[31] We studied rats on a normal salt diet, with 5/6 nephrectomy produced by uninephrectomy, and ligation of 2 to 3 branches of renal artery of the contralateral kidney. Hyperuricemia was induced in 2 groups of rats by administering intragastric OA. To prevent the increment of SUA, one group received allopurinol in the drinking water. A third group served as control. Animals were studied after 30 days. OA administration induced a 2-fold increase of SUA that was prevented by allopurinol. Control 5/6 nephrectomy rats developed severe hyperten-

sion and proteinuria, which increased further with hyperuricemia and was restored to control values by allopurinol treatment.

The main finding of these studies was that mild hyperuricemia produced profound renal cortical vasoconstriction. Single-nephron glomerular plasma flow and GFR decreased by 40%; the ultrafiltration coefficient also decreased in the same proportion. Afferent and efferent resistances increased by 2-fold. Despite intense vasoconstriction, glomerular hypertension was unchanged in hyperuricemic rats. Morphometric analysis of the afferent arteriole in control 5/6 nephrectomy rats revealed hypertrophy of the vascular wall. However, the increase in SUA level markedly accentuated the arteriolopathy, with increasing arteriolar thickening and a 30% increase in the media to lumen ratio. Allopurinol treatment partly restored the functional changes, however, it fully prevented the arteriolopathy. Arteriolar wall thickness was normal and the media to lumen ratio was significantly lower than the hyperuricemic and control groups. Interestingly, preservation of vascular structure was associated with maintaining normal glomerular pressure despite systemic hypertension, which denotes a normal autoregulatory response of preglomerular vessels to the increase of arterial pressure.[31] The contribution of preglomerular vascular lesion to the increment of glomerular capillary pressure was evidenced further by a positive significant correlation of individual values of media to lumen ratio and glomerular pressure in the 3 groups of rats. In addition, a significant positive correlation was found between individual values of serum uric acid and media to lumen ratio, underscoring the role of uric acid in stimulating proliferation of vascular smooth muscle cells.[31]

In conclusion, owing to the proliferative effect of uric acid on vascular smooth muscle cells, chronic mild hyperuricemia produces renal arteriolopathy. The consequences of the vascular lesion are, on the one hand, an impaired capacity of preglomerular vessels to maintain constancy of glomerular pressure in the face of arterial hypertension causing (normal rats) or perpetuating (5/6 nephrectomy rats) glomerular hypertension. On the other hand, lumen obliteration induced by vascular wall thickening results in severe vasoconstriction, decreasing renal plasma flow, GFR, and perfusion to peritubular capillaries. The resulting ischemia is a potent stimulus that induces tubulointerstitial inflammation and fibrosis as well as arterial hypertension. Evidence for these alterations is provided by studies in which mild hyperuricemia was responsible for later development of salt-sensitive hypertension in normal rats.[32] Furthermore, it is possible that as the arteriolar changes become more severe, glomerular ischemia and eventual collapse with a decrease in glomerular pressure could take place, as has been postulated to occur with prolonged and severe hypertension.[33] Thus, these studies provide a potential mechanism by which hyperuricemia can mediate hypertension and renal disease.

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