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ACTIVATION OF THE INTRARENAL RENIN-ANGIOTENSIN SYSTEM IN THE DEVELOPMENT OF GLOMERULOSCLEROSIS IN HYPERURICEMIA

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Annotation: Hyperuricemia is increasingly recognized as a major factor in the development of chronic kidney disease and glomerular injury. Elevated serum uric acid not only causes direct nephron damage but also activates the intrarenal renin-angiotensin system (RAS), leading to increased angiotensin II production. This activation elevates glomerular pressure, stimulates mesangial cell proliferation, and promotes extracellular matrix accumulation, resulting in progressive glomerulosclerosis. Oxidative stress, inflammatory cytokines, and fibrotic signaling pathways further exacerbate renal injury. Clinical and experimental evidence indicates that interventions targeting uric acid reduction and RAS inhibition can attenuate glomerular damage and slow the progression of kidney disease. Understanding the mechanisms linking hyperuricemia and intrarenal RAS activation is essential for the development of preventive and therapeutic strategies aimed at preserving renal function.

Keywords: Hyperuricemia, intrarenal renin-angiotensin system, glomerulosclerosis, angiotensin II, oxidative stress, inflammation, fibrosis.

Introduction

Hyperuricemia, characterized by elevated serum uric acid levels, is increasingly recognized as a significant contributor to kidney injury and chronic renal disease. Beyond its direct nephrotoxic effects, hyperuricemia activates the intrarenal renin-angiotensin system (RAS), which plays a central role in the regulation of renal hemodynamics and structural integrity. Activation of intrarenal RAS leads to increased production of angiotensin II, a potent vasoconstrictor, resulting in elevated glomerular capillary pressure and subsequent mechanical stress on glomerular cells. Angiotensin II also stimulates mesangial cell proliferation and promotes extracellular matrix accumulation, key events in the development of glomerulosclerosis. Moreover, RAS activation enhances pro-inflammatory and pro-fibrotic signaling pathways, further accelerating renal tissue remodeling and functional decline. Experimental studies suggest that hyperuricemia-induced oxidative stress may synergize with RAS activation, amplifying glomerular injury. Clinically, this combination contributes to the progressive deterioration of kidney function, often preceding overt chronic kidney disease. Understanding the molecular and cellular mechanisms linking hyperuricemia, intrarenal RAS activation, and glomerular sclerosis is critical for identifying potential therapeutic targets. Interventions aimed at modulating RAS activity or reducing uric acid levels may therefore provide effective strategies to prevent or slow the progression of glomerular damage. In this

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context, exploring the interplay between metabolic factors and intrarenal RAS is essential for advancing kidney disease management.

Main part

Hyperuricemia, or elevated serum uric acid levels, is a recognized risk factor for kidney injury and glomerular pathology. Excess uric acid induces endothelial dysfunction, oxidative stress, and local inflammation within renal tissues. The intrarenal renin-angiotensin system (RAS) plays a central role in maintaining glomerular hemodynamics and structural integrity. Hyperuricemia stimulates the activation of intrarenal RAS, resulting in increased angiotensin II production. Angiotensin II acts as a potent vasoconstrictor, elevating glomerular capillary pressure and causing mechanical stress on glomerular cells. This stress promotes mesangial cell proliferation and hypertrophy, contributing to early glomerular injury. Angiotensin II also induces extracellular matrix deposition, which is a key factor in the development of glomerulosclerosis. Pro-inflammatory cytokines, such as TNF- α and IL-6, are upregulated in response to RAS activation, while fibrotic mediators like TGF- β 1 enhance matrix accumulation. Oxidative stress associated with hyperuricemia synergizes with RAS activity, amplifying cellular damage. Podocyte injury occurs due to both mechanical stress and angiotensin II-mediated signaling. Endothelial dysfunction further impairs nitric oxide availability, worsening glomerular perfusion. Local expression of renin and angiotensinogen is increased, creating a positive feedback loop that perpetuates RAS activation. Glomerular basement membrane thickening and sclerosis develop as a consequence of these combined effects. Experimental studies show that RAS blockade reduces hyperuricemia-induced glomerular injury. Clinical evidence supports the use of ACE inhibitors and ARBs in slowing progression of renal damage in hyperuricemic patients. Understanding these mechanisms is essential for the identification of potential therapeutic targets and strategies for preventing glomerulosclerosis.

Hyperuricemia is closely associated with impaired renal function and progression of chronic kidney disease. Elevated uric acid levels correlate with increased intraglomerular pressure and proteinuria, reflecting early glomerular damage. Activation of the intrarenal RAS is a key mediator linking hyperuricemia to glomerular pathology. Angiotensin II not only increases vascular resistance but also promotes mesangial expansion and extracellular matrix deposition. Biochemical studies indicate that hyperuricemia triggers oxidative stress, lipid peroxidation, and endothelial cell dysfunction. These processes enhance inflammatory signaling within the glomeruli, including upregulation of TNF- α , IL-1 β , and other pro-inflammatory mediators. Elevated uric acid also stimulates TGF- β 1 and connective tissue growth factor (CTGF), further promoting fibrosis. Clinically, patients with hyperuricemia often demonstrate microalbuminuria or mild proteinuria before any decline in glomerular filtration rate becomes apparent. Laboratory findings reveal increased plasma renin activity and elevated angiotensin II levels in such patients, supporting the link between metabolic disturbance and RAS activation. Therapeutic interventions targeting uric acid reduction and RAS inhibition have shown improvements in renal hemodynamics and attenuation of glomerulosclerosis. Early identification of biochemical markers associated with hyperuricemia and RAS activity can guide effective clinical management. Moreover, ongoing monitoring of uric acid and RAS parameters may help predict disease progression. Understanding these relationships provides a foundation for integrated therapeutic approaches to preserve renal function.

Given the pathogenic role of hyperuricemia-induced RAS activation in glomerulosclerosis, therapeutic strategies focus on both uric acid reduction and modulation of the RAS. Pharmacological agents such as xanthine oxidase inhibitors reduce serum uric acid levels and diminish oxidative stress in renal tissues. Simultaneously, ACE inhibitors and angiotensin receptor blockers (ARBs) directly suppress angiotensin II activity, alleviating glomerular

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hypertension and preventing mesangial proliferation. Combination therapy has been shown to synergistically protect against glomerular injury in experimental models. Lifestyle modifications, including dietary purine restriction, weight management, and increased hydration, also contribute to lowering uric acid levels and reducing renal stress. Regular monitoring of renal function, serum uric acid, and markers of RAS activity is essential to evaluate therapeutic efficacy. Early intervention is particularly effective in preventing irreversible glomerular damage and slowing the progression of chronic kidney disease. Future research focuses on novel agents targeting specific molecular pathways, including TGF- β signaling and oxidative stress mediators. Personalized medicine approaches may optimize treatment based on individual biochemical profiles and RAS activity. Preventive strategies combined with pharmacological intervention have the potential to substantially reduce the burden of hyperuricemia-related renal disease. Understanding the interplay between metabolic factors and intrarenal RAS is key to improving long-term renal outcomes.

Conclusion

Hyperuricemia plays a critical role in the development of glomerular injury through both direct nephrotoxic effects and the activation of the intrarenal renin-angiotensin system (RAS). Activation of RAS increases angiotensin II production, leading to elevated glomerular pressure, mesangial cell proliferation, extracellular matrix accumulation, and progressive glomerulosclerosis. The interplay between oxidative stress, inflammation, and fibrotic signaling pathways further exacerbates renal tissue remodeling and functional decline. Clinical and experimental evidence indicates that interventions targeting uric acid reduction, RAS inhibition, or both can significantly attenuate glomerular damage and slow the progression of chronic kidney disease. Understanding the molecular and cellular mechanisms linking hyperuricemia and intrarenal RAS activation provides critical insights for developing effective preventive and therapeutic strategies. Early detection and targeted management are essential to preserve renal function and prevent irreversible glomerular sclerosis in hyperuricemic patients.

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