PATHOPHYSIOLOGICAL AND MOLECULAR MECHANISMS OF RENAL DYSFUNCTION IN URETERAL STONE-INDUCED OBSTRUCTION

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Abstract

Ureteral stone-induced obstruction is one of the most common causes of obstructive nephropathy and may lead to progressive deterioration of renal function. The pathological processes associated with urinary tract obstruction are not limited to the mechanical impairment of urine flow but also involve complex hemodynamic, cellular, and molecular alterations. Increased intrapelvic pressure results in a reduction of glomerular filtration rate, decreased renal blood flow, and tissue hypoxia. Under hypoxic and ischemic conditions, activation of the renin–angiotensin–aldosterone system, oxidative stress pathways, NF-κB-mediated inflammatory responses, and TGF-β1/Smad signaling occurs. These processes contribute to tubular epithelial cell injury, epithelial–mesenchymal transition, excessive extracellular matrix deposition, and the development of tubulointerstitial fibrosis. Progressive fibrosis is associated with nephron loss and the subsequent development of chronic kidney disease. Early detection of ureteral stones and timely relief of obstruction remain essential for preserving renal function. A comprehensive understanding of the molecular mechanisms involved in obstructive nephropathy may facilitate the development of novel pathogenetically targeted therapeutic strategies.

Keywords: ureteral stone, obstructive nephropathy, renal function, renin–angiotensin–aldosterone system, oxidative stress, NF-κB, TGF-β1, epithelial–mesenchymal transition, tubulointerstitial fibrosis.

Introduction. Urolithiasis is one of the most prevalent urological disorders worldwide. Its high incidence, tendency to recur, and potential to contribute to chronic kidney disease highlight its significant clinical and socioeconomic burden. A substantial proportion of urinary calculi are localized within the ureter, where they may partially or completely obstruct urine flow. Consequently, obstructive nephropathy develops, leading to both functional and structural alterations within the renal parenchyma [1,2].

In the early stages of obstruction, hydrostatic pressure increases within the collecting system, resulting in a decline in glomerular filtration rate and disruption of intrarenal hemodynamics. However, the progression of renal injury cannot be explained solely by mechanical factors. Complex molecular and cellular responses are triggered within the renal tissue, involving tissue hypoxia, oxidative stress, and increased expression of inflammatory mediators. These processes compromise nephron integrity and promote fibrotic remodeling [3,4].

Recent advances in renal pathophysiology have emphasized the pivotal role of the renin–angiotensin–aldosterone system (RAAS), transforming growth factor-beta (TGF-β1), nuclear factor-kappa B (NF-κB), hypoxia-inducible factors, and epithelial–mesenchymal transition in the progression of obstructive nephropathy. Interactions among these molecular pathways contribute to tubulointerstitial fibrosis and may ultimately result in irreversible renal failure [5,6].

The aim of this study was to analyze the principal pathophysiological and molecular mechanisms responsible for renal function impairment in ureteral stone-induced obstruction.

Materials and Methods. This study was conducted as a narrative review of contemporary scientific literature. Current evidence regarding the

pathophysiological and molecular mechanisms of renal function impairment in ureteral stone-associated obstructive nephropathy was systematically evaluated.

Particular attention was paid to intrarenal hemodynamic alterations, activation of the renin–angiotensin–aldosterone system, oxidative stress, inflammatory responses, hypoxia-related signaling pathways, TGF-β1/Smad signaling, epithelial–mesenchymal transition, and the molecular basis of tubulointerstitial fibrosis. The collected data were critically analyzed, compared, and synthesized to provide a comprehensive overview of the mechanisms underlying obstructive renal injury.

Results. The development of ureteral obstruction leads to a progressive increase in hydrostatic pressure within the renal collecting system. Elevated pressure within Bowman's capsule contributes to a decline in glomerular filtration rate. Simultaneously, alterations in afferent and efferent arteriolar tone reduce renal blood flow and promote tissue hypoxia [2,3].

Reduced renal perfusion triggers activation of the renin–angiotensin–aldosterone system. Excessive production of angiotensin II not only enhances vasoconstriction and ischemia but also stimulates TGF-β1 expression, thereby promoting fibrogenic pathways [4,5].

Obstructive conditions are associated with increased generation of reactive oxygen species. Oxidative stress induces damage to cellular membranes, proteins, and nucleic acids. Furthermore, disruption of mitochondrial membrane potential impairs ATP synthesis and activates apoptotic pathways in tubular epithelial cells [6].

The inflammatory response is intensified through activation of the NF-κB signaling pathway. This transcription factor promotes the synthesis of pro-inflammatory mediators, including TNF-α, IL-1β, IL-6, and MCP-1. Consequently, macrophage infiltration and recruitment of other immune cells into the renal interstitium increase, leading to the establishment of a chronic inflammatory microenvironment [7].

TGF-β1/Smad signaling plays a central role in renal fibrogenesis. Activation of Smad2 and Smad3 signaling pathways enhances the synthesis of collagen types I and III as well as fibronectin. Excessive accumulation of extracellular matrix components contributes to the development of tubulointerstitial fibrosis [5,8].

Prolonged exposure to TGF-β1 promotes epithelial–mesenchymal transition, during which tubular epithelial cells lose their epithelial characteristics and acquire fibroblast-like phenotypes. This process accelerates fibrotic remodeling and contributes to irreversible structural damage within the renal parenchyma [8,9].

Discussion. Obstructive nephropathy caused by ureteral stones represents a multifactorial pathological condition in which mechanical, hemodynamic, and molecular factors interact within a unified pathogenic framework. While increased intrapelvic pressure initiates the early functional disturbances, subsequent cellular and molecular responses determine the progression and severity of renal injury.

Tissue hypoxia and oxidative stress are closely interconnected processes that disrupt cellular metabolism and enhance the production of inflammatory mediators. From this perspective, renal injury in obstructive nephropathy should not be regarded as a passive consequence of mechanical obstruction but rather as an active biological process characterized by sustained cellular responses.

The interaction among the renin–angiotensin–aldosterone system, NF-κB signaling, and TGF-β1-mediated pathways represents a critical determinant of fibrosis progression. Mutual amplification among these pathways establishes a pathogenic cycle that perpetuates inflammation and extracellular matrix deposition. This phenomenon may explain why complete recovery of renal function is not always achieved even after relief of obstruction.

Tubulointerstitial fibrosis represents the final common pathway of obstructive nephropathy. The extent of fibrosis is closely associated with nephron loss and the progression of chronic kidney disease. Therefore, current therapeutic approaches

should focus not only on relieving obstruction but also on targeting the molecular mechanisms responsible for inflammation, oxidative stress, and fibrogenesis.

Conclusion. Ureteral stone-induced obstruction is characterized by complex and multistage pathogenic mechanisms leading to renal function impairment. Altered intrarenal hemodynamics, tissue hypoxia, activation of the renin–angiotensin–aldosterone system, oxidative stress, and inflammatory responses play crucial roles in disease progression.

Activation of NF-κB and TGF-β1/Smad signaling pathways constitutes the principal molecular basis of tubulointerstitial fibrosis. Epithelial–mesenchymal transition and excessive extracellular matrix accumulation contribute to irreversible structural changes within the renal parenchyma.

In addition to early diagnosis and timely relief of urinary tract obstruction, therapeutic strategies targeting inflammation, oxidative stress, and fibrogenic signaling pathways may represent promising approaches for the prevention and treatment of obstructive nephropathy.

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