PATHOPHYSIOLOGICAL MECHANISMS UNDERLYING RENAL PARENCHYMAL INJURY IN HYDRONEPHROSIS

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Abstract

Hydronephrosis is a pathological condition characterized by dilation of the renal collecting system and progressive injury to the renal parenchyma as a consequence of urinary tract obstruction. The development and progression of hydronephrosis involve a complex interplay of increased intrarenal pressure, hemodynamic disturbances, tissue hypoxia, oxidative stress, inflammatory responses, and fibrotic remodeling. The severity and duration of urinary tract obstruction determine the extent of structural and functional alterations within the renal parenchyma. At the molecular level, activation of the renin–angiotensin–aldosterone system (RAAS), TGF-β1/Smad signaling, NF-κB-mediated inflammatory pathways, and mitochondrial dysfunction play crucial roles in disease progression. This study analyzes the principal pathophysiological and molecular mechanisms underlying renal parenchymal injury in hydronephrosis. A comprehensive understanding of these mechanisms may facilitate the development of novel therapeutic strategies aimed at preventing irreversible loss of renal function.

Keywords: hydronephrosis, obstructive nephropathy, renal parenchyma, hypoxia, oxidative stress, TGF-β1, NF-κB, fibrosis, chronic kidney disease.

Introduction. Hydronephrosis is a pathological condition that develops as a result of partial or complete impairment of urinary flow and is characterized by progressive damage to the renal parenchyma. This condition may arise secondary to

urolithiasis, ureteral strictures, congenital anomalies, malignancies, and other obstructive disorders of the urinary tract [1].

Although hydronephrosis is initially characterized by increased mechanical pressure within the collecting system, the subsequent progression of renal injury is largely determined by complex molecular and cellular mechanisms. Tissue hypoxia, microcirculatory disturbances, inflammatory responses, and fibrogenesis contribute significantly to progressive nephron loss and deterioration of renal function [2].

Current understanding of hydronephrosis has evolved considerably over recent years. Renal injury is no longer regarded solely as a consequence of mechanical obstruction but rather as a multifaceted process involving immune-mediated inflammation and molecular remodeling. In particular, activation of the renin–angiotensin–aldosterone system (RAAS), TGF-β1 signaling, oxidative stress, and epithelial–mesenchymal transition have emerged as critical contributors to disease progression [3,4].

The aim of this study was to analyze the principal pathophysiological and molecular mechanisms underlying renal parenchymal injury in hydronephrosis.

Materials and Methods. The theoretical framework of this study was based on contemporary scientific evidence regarding the pathogenesis of hydronephrosis and obstructive nephropathy. Particular attention was focused on intrarenal hemodynamics, hypoxia-associated signaling pathways, activation of the renin–angiotensin–aldosterone system, oxidative stress, inflammatory mediators, mitochondrial dysfunction, and mechanisms of fibrosis.

In addition, the roles of TGF-β1/Smad signaling, NF-κB-mediated inflammatory responses, epithelial–mesenchymal transition, and extracellular matrix accumulation in renal parenchymal injury were critically evaluated using comparative and analytical approaches.

Results. During the early stages of hydronephrosis, increased intrapelvic pressure leads to a reduction in glomerular filtration rate and renal blood flow.

Impaired renal perfusion subsequently contributes to the development of chronic tissue hypoxia [2,5].

Under hypoxic conditions, hypoxia-inducible factor-1 alpha (HIF-1α) becomes activated, initiating adaptive metabolic responses within renal cells. However, prolonged hypoxia results in mitochondrial dysfunction and bioenergetic failure, ultimately promoting apoptosis of tubular epithelial cells [6].

Renal parenchymal injury is also closely associated with activation of the renin–angiotensin–aldosterone system. Through stimulation of angiotensin II type 1 (AT1) receptors, angiotensin II promotes vasoconstriction, oxidative stress, and inflammatory responses. Furthermore, it enhances TGF-β1 expression, thereby stimulating fibrogenic pathways [3,7].

Oxidative stress represents a major component of hydronephrosis pathogenesis. Activation of NADPH oxidase leads to excessive generation of reactive oxygen species, resulting in damage to cellular membranes, proteins, and DNA. These alterations further amplify inflammatory responses and accelerate tissue injury [8].

Activation of the NF-κB signaling pathway increases the secretion of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. Consequently, infiltration of macrophages and other immune cells into the renal interstitium is enhanced, establishing a persistent inflammatory microenvironment [4].

Fibrosis represents the final and prognostically most significant stage of hydronephrosis. Activation of the TGF-β1/Smad signaling pathway increases the synthesis of collagen type I, collagen type III, and fibronectin. Simultaneously, epithelial–mesenchymal transition contributes to fibroblast accumulation and excessive extracellular matrix deposition, ultimately leading to tubulointerstitial fibrosis [7,9].

Discussion. Renal parenchymal injury in hydronephrosis results from a complex network of interconnected pathophysiological mechanisms. Although

mechanical obstruction initiates the pathological process, subsequent disease progression is primarily driven by cellular and molecular alterations.

The interaction between tissue hypoxia and oxidative stress represents one of the principal determinants of parenchymal injury. Mitochondrial dysfunction impairs cellular energy metabolism, reduces regenerative capacity, and enhances apoptotic pathways. Therefore, explaining hydronephrosis solely in terms of mechanical obstruction fails to capture the complexity of its pathogenesis.

The molecular interplay between RAAS activation and TGF-β1 signaling constitutes a central mechanism of fibrogenesis. These signaling networks collectively sustain chronic inflammation and extracellular matrix accumulation. Consequently, complete recovery of renal function may not occur even after successful relief of urinary tract obstruction.

Recent therapeutic approaches have shifted beyond simple elimination of obstruction and increasingly focus on targeting fibrogenesis, oxidative stress, and inflammatory pathways. Such strategies may offer greater potential for preserving renal parenchymal integrity and preventing irreversible renal damage.

Conclusion. Renal parenchymal injury in hydronephrosis develops through interconnected mechanisms involving increased intrarenal pressure, tissue hypoxia, oxidative stress, inflammation, and fibrogenesis.

The renin–angiotensin–aldosterone system, NF-κB signaling, and TGF-β1/Smad pathways represent key molecular regulators of renal injury. These mechanisms form the pathophysiological basis of tubulointerstitial fibrosis and chronic kidney disease progression.

A deeper understanding of these pathogenic pathways may provide the foundation for the development of novel diagnostic and therapeutic approaches aimed at preserving renal function in patients with hydronephrosis.

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