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Pathophysiological mechanisms of renal damage in obstructive uropathies as potential therapeutic targets: A literature review

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Abstract

Obstructive uropathies are a group of conditions characterized by urinary tract blockages, leading to impaired urine flow and renal damage. This comprehensive literature review aims to explore the pathophysiological mechanisms underlying renal damage in obstructive uropathies and identify potential therapeutic targets for intervention. The review synthesizes current knowledge from a wide range of studies and provides an overview of the complex cellular and molecular processes involved in renal damage progression, including hemodynamic alterations, oxidative stress, interstitial inflammation, and tubulointerstitial fibrosis. Key players in the pathogenesis of renal damage, such as the renin-angiotensin-aldosterone system, reactive oxygen species, immune cells, and fibrogenic factors, are discussed in detail. Furthermore, potential therapeutic targets, including renin-angiotensin inhibitors, antioxidants, anti-inflammatory agents, and anti-fibrotic strategies, are identified based on preclinical and experimental studies. Additionally, emerging therapeutic modalities like mesenchymal stem cells and extracellular vesicles derived from MSCs are explored for their potential in attenuating renal damage and promoting tissue repair. Understanding the pathophysiological mechanisms and identifying potential therapeutic targets is crucial for the development of effective interventions to mitigate renal damage in obstructive uropathies, ultimately improving patient outcomes and quality of life. Further research and clinical trials are needed to translate these promising findings into clinical practice and address the unmet therapeutic needs in this patient population.

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Introduction

Congenital obstructive uropathies are a group of conditions that affect the urinary system in children, leading to blockages or obstructions in the urinary tract and impaired urine flow. These conditions have a prevalence ranging from 1% to 5.4% in the overall child population (1). In childhood, congenital urinary tract obstruction (CUTO) accounts for up to 50% (46-59%) of chronic kidney disease (CKD) cases (2). Children with CUTO are at risk of developing end-stage CKD, which is the most severe and advanced stage of kidney disease. The likelihood of progression to end-stage CKD depends on various factors, including the anatomical variations of the urinary tract obstruction, genetic characteristics influencing the disease course, treatment methods employed, and social factors (3). Assessing the severity of morphological damage to renal tissue and the functional potential of the kidneys is crucial in determining the quality of life for children with obstructive uropathies.

The socio-economic impact of CKD is substantial, as it requires significant financial resources throughout the various stages of treatment, including the end-stage of chronic kidney insufficiency, where dialysis or kidney transplantation may be necessary. Given the complexity of CKD and the challenges in its treatment, it is evident that identifying promising approaches to tackle renal fibrosis and CKD requires the expertise of specialists in fundamental science. Understanding the pathogenesis and progression of fibrotic changes in the kidneys associated with CUTO is essential in addressing this problem comprehensively (4,5).

Currently, available treatment options for CKD are limited and often ineffective, particularly in terms of targeting and slowing down or reversing renal fibrosis Moreover, there is a lack of targeted therapies that can effectively tackle this aspect of the disease (3).

Therefore, fundamental science and research play a vital role in identifying innovative approaches to address renal fibrosis and CKD effectively. This review aimed to provide a comprehensive understanding of the pathogenesis and progression of renal damage in obstructive uropathies, particularly in the context of CKD (4-6).

Renal damage in congenital obstructive uropathies

Obstructive uropathy, which refers to the obstruction of the urinary tract, is the primary identifiable cause CKD in children. The obstruction of the urinary tract during prenatal development can have damaging effects on the kidneys, leading to secondary changes in renal parenchyma, which includes the glomerular and tubular apparatus of the kidneys (4). These changes result in a reduction in the number of nephrons, impaired kidney growth, and the development of tubulointerstitial damage, which, in turn, leads to renal fibrosis.

Parenchymal damage can occur in cases of both single and recurrent hydrostatic injuries resulting from various forms of urinary tract obstruction. These obstructions can be anatomical, such as ureteral stenosis, or functional, including conditions like vesicoureteral reflux and neurogenic bladder dysfunction (4,5,7,8).

These conditions can lead to direct damage to the renal parenchyma. Hydronephrosis, which occurs due to obstruction of the pyeloureteral segment of the ureter, leads to a significant increase in intrapelvic pressure (5,9,10). This causes dilation and rupture of tubules, resulting in damage to the tubular epithelial cells (TECs). The reflux of urine and its drainage through the venous and lymphatic systems of the obstructed kidney contribute to decreased urine production and reduced intraluminal pressure, which can be considered as compensatory mechanisms to limit the damaging effects of urodynamic obstruction (4,5,7). Recent evidence suggests that proximal TECs, instead of being mere victims of destruction, play a crucial role in both CKD progression and kidney recovery. They are actively involved in various cellular interactions that contribute to the damage of the obstructed kidney, ultimately leading to interstitial fibrosis (3,7,11).

Renal fibrosis is a common outcome in various types of progressive nephropathies, regardless of their underlying causes. In recent years, there has been a shift in the focus of studying the pathogenesis of renal damage from glomerulosclerosis and interstitial fibrosis, which are morphological characteristics of the end-stage of CKD, to the proximal tubules as key players in CKD progression (5). The proximal tubules, which are abundant in mitochondria and rely on oxidative phosphorylation, have a high rate of oxygen consumption. However, their relatively weak endogenous antioxidant defense mechanisms make them particularly susceptible to damage from obstructions, ischemia, hypoxia, oxidative stress, toxins and metabolic disturbances (5,7,8).

Unilateral ureteral obstruction (UUO) has become the most commonly used animal model for studying progressive CKD over the past three decades. The advancement of molecular diagnostic methods has enabled the identification of numerous cellular interactions that contribute to the damage observed in the obstructed kidney, with interstitial fibrosis being the ultimate result (11-13). In cases of UUO, the destruction of glomerulotubular junctions and the eventual formation of atubular glomeruli were essential steps in parenchymal damage. This process is not specific to "tubulointerstitial diseases" alone, such as polycystic kidney disease, but can also occur in "glomerular diseases" like congenital nephrotic syndrome and diabetic nephropathy (11,14).

Animal models of UUO have demonstrated that a combination of obstructive and ischemic renal damage contributes to the development of congenital obstructive nephropathy (15-17). Ischemia and oxidative stress result in the death of proximal tubular cells, leading to the subsequent development of interstitial fibrosis. In adult mice, complete unilateral obstruction of the ureter (CUUO) leads to a rapid loss of renal parenchyma. This loss is primarily attributed to a significant reduction (around 65%) in the mass of proximal tubules, which occurs due to various forms of cell death, including necrosis, apoptosis, and autophagy. However, congenital obstructive nephropathy typically arises from partial rather than complete ureteral obstruction. Partial obstruction allows for a gradual development of renal cellular reactions. To study the effects of congenital obstructive nephropathy, researchers often employ a model of partial unilateral obstruction of the ureter (PUUO) in neonatal rats (4,5). This model is chosen because nephrogenesis in rodents continues for approximately one week after birth, and nephron maturation occurs during the subsequent week. Therefore, kidney development in rodents during this timeframe is comparable to human kidney development during the second trimester of pregnancy and at birth (16,17). Using the PUUO model in neonatal rats, researchers have found that obstructing the ureter in the early stages of kidney development hampers normal kidney maturation and growth. This obstruction also leads to early loss of nephrons. Importantly, the PUUO model allows for the observation of various stages of kidney recovery following the removal of the ureteral obstruction. Overall, animal models of UUO, particularly using partial unilateral obstruction, provide valuable insights into the pathogenesis and progression of congenital obstructive nephropathy (18-20). They help researchers understand the cellular reactions, loss of nephrons, and subsequent recovery stages associated with obstructive uropathies, ultimately contributing to the development of potential therapeutic approaches for improving outcomes in affected individuals.

Many authors have highlighted various mechanisms that play a crucial role in the development of obstructive kidney damage resulting from obstruction (5,7,21). These mechanisms encompass a range of pathological processes. Firstly, hemodynamic component - insufficient perfusion, leads to tubular ischemia, causing a lack of adequate blood supply to the tubular structures. Secondly, interstitial inflammation occurs as a response to the obstruction, contributing to tissue damage. The mechanical compression imposed by the obstruction itself also contributes to the detrimental effects on TECs. Furthermore, tubular cell apoptosis, a form of programmed cell death, is observed in obstructive kidney damage. The obstruction-induced stress triggers oxidative stress within the renal tissue, leading to cellular damage. Lastly, tubulointerstitial fibrosis (TIF), characterized by the excessive accumulation of extracellular matrix components, is a significant consequence of obstructive kidney damage. Collectively, these pathological processes—tubular ischemia and oxidative stress, interstitial inflammation, mechanical compression and TEC damage, and tubulointerstitial fibrosis—mediate the renopathogenic effects associated with obstruction-induced kidney damage (4,5,7,11,14,18,21,22).

The hemodynamic response of the RAAS to CUUO. Oxidative stress

According to Chevalier et al. (4) the initial response to the increased pressure within the urinary tract is the activation of the renin-angiotensin-aldosterone system (RAAS). The main mediator in the pathogenesis of obstructive nephropathy is angiotensin II, whose expression is believed to contribute to a significant portion of renal fibrosis in chronic neonatal obstructive uropathy (4,5,7,8,11,21,23-26).

Initially, there is a transient increase in renal blood flow due to the production of vasodilators. However, the intrarenal RAAS is subsequently activated, leading to vasoconstriction of both the pre- and postglomerular arterioles. This results in reduced renal blood flow, decreased oxygen levels in the renal tissue, and a decline in glomerular filtration rate (GFR) (27-29).

Angiotensin II acts primarily through the AT1 receptors and stimulates the production of reactive oxygen

species (ROS) through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (30). This oxidative stress involves an excessive production of ROS, including superoxide anion, hydrogen peroxide, and hydroxyl anion. Mitochondria, which are responsible for energy production through oxidative phosphorylation in the kidneys, play a crucial role in this process. Impairment of energy production processes and mitochondrial dysfunction contribute to the decrease in NADPH oxidase levels and excessive production of ROS in renal tubular epithelial cells (TECs), leading to oxidative stress. (31) This oxidative stress is implicated in the pathogenesis of obstructive nephropathy and the subsequent development of fibrosis. Understanding the involvement of the RAAS and the generation of ROS in obstructive nephropathy provides insights into potential therapeutic targets for mitigating renal damage and fibrosis in cases of urinary tract obstruction (4,5,7,32).

According to researchers (7,30,31), oxidative stress plays a significant role in the progression of chronic kidney disease (CKD) by exerting various effects. Activation of the intrarenal renin-angiotensin system contributes to tubular and interstitial damage, as demonstrated by studies showing a strong correlation between damage and the number of angiotensinogen gene copies in transgenic mice (30,33,34). Reactive oxygen species (ROS) function as secondary messengers essential for cellular homeostasis, and their concentration, production, and elimination are tightly regulated by the antioxidant system. Imbalances in the antioxidant system lead to mitochondrial dysfunction, reduced antioxidant capacity, irreversible protein oxidation, and the stimulation of inflammatory molecules such as interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule-1 (VCAM-1), and tumor necrosis factor-alpha (TNF-α). This promotes leukocyte migration and proliferation, increases the levels of fibrotic and inflammatory proteins, activates transforming growth factor-beta 1 (TGF-β1) and nuclear factor kappa B (NF-κB), and disrupts the production of vascular endothelial growth factor (VEGF), ultimately exacerbating peritubular capillary damage (30,35,36). Oxidative stress-induced cytokine production leads to inflammatory and profibrotic effects, ultimately causing cell death through apoptosis or necrosis. This process results in segment-specific ischemic injury with subsequent necrosis of proximal tubules and disruption of glomerulotubular connections, leading to the formation of atubular glomeruli. These events contribute to the development of tubulointerstitial fibrosis (37-39).

An important observation is that in newborn mice, which have incomplete nephrogenesis and tubular cell mitochondrial maturation at birth, their energy metabolism is glycolytic and anaerobic (5). Unlike in adult individuals, complete oxidative metabolism does not cause tubular cell death until mitochondrial maturation is complete and the energy metabolism switches from glycolytic to oxidative. In experiments involving newborn mice with complete ureteral obstruction, there was a four-fold increase in glycolytic metabolism in proximal tubules compared to adult individuals. The suppression of oxidative mitochondrial metabolism in response to ureteral obstruction was considered an adaptive response in these newborn mice.

Proximal tubules have a high demand for ATP to perform crucial functions such as reabsorption of glucose, ions, and nutrients, as well as the operation of the Na-K pump (5,30). However, they are more vulnerable to ischemic and toxic damage compared to distal tubules due to their limited capacity for anaerobic glycolytic ATP production and the absence of certain protective proteins.

When diffuse chronic kidney damage occurs, there is a suppression of energy exchange, which leads to an increase in metabolism in healthy nephrons. However, this sustained activation of oxygen consumption by hypertrophied proximal tubules may be unstable and contribute to the progression of chronic kidney disease or aging (3,5,30,40).

ATP not only serves as an energy source but also plays a regulatory role in activating signaling pathways involved in various cellular processes such as growth, differentiation, apoptosis, inflammation, fibrosis, and epithelial-mesenchymal transition (EMT). Mitochondrial ATP levels play a role in promoting the differentiation of macrophages into the profibrotic M2 phenotype, contributing to inflammation. This process also activates myofibroblasts, which replace lost epithelial cells with extracellular matrix, leading to progressive fibrosis in the kidneys (41). The activation of the intrarenal RAAS is a commonly used therapeutic approach for managing chronic kidney disease. Drugs that inhibit angiotensin-converting enzyme and block AT1 and AT2 receptors are employed to improve tubular function by enhancing regional blood flow and glomerular filtration rate. Partial ureteral obstruction in developing kidneys leads to pathological changes such as tubulointerstitial infiltrate, tubular apoptosis with the formation of atubular glomeruli, and tubulointerstitial fibrosis. However, the precise understanding of all aspects of these changes is still limited (21,42).

Interstitial inflammation and fibrosis

In cases of obstructive uropathy, the increase in intracavitary hydrostatic pressure causes mechanical damage to proximal tubules, leading to their distension, compression, and rupture. Tubuloepithelial cells (TECs) in response to urinary tract obstruction exhibit innate immune characteristics and act as inflammatory and fibrogenic cells. They release various signaling molecules, including cytokines, chemokines, growth factors, and enzymes, attracting leukocytes and promoting tubulointerstitial inflammation and subsequent fibrosis (3-5).

Tubulointerstitial inflammation is observed (7,11,19) in the early stages of many kidney diseases, and failure to eliminate the cause and restore damaged tubules properly can result in the progression of CKD. Damaged TECs further enhance the immune response by producing pro-inflammatory cytokines, such as IL-1β, IL-18, IL-6, IL-15, IL-16, IL-34, TNF-α, Fas ligand, CTGF, VEGF, and CSF-1 (5, 20). Factors like chemokines, intercellular adhesion molecule 1 (ICAM-1), IL-1, MCP-1, CSF-1, and cell adhesion molecules contribute to leukocyte influx, macrophage stimulation, and proliferation at the site of injury (21,22,43). Chemokines, particularly CCL2, produced by tubulointerstitial epithelial cells, play a role in promoting tubulointerstitial inflammation and attracting specific immune cells such as neutrophils. The induction of chemokines is regulated by various signaling pathways (12).

Cell adhesion molecules play a crucial role in maintaining the integrity and polarity of renal epithelial cells, ensuring normal solute secretion and reabsorption. ICAM-1 and selectins derived from tubulointerstitial epithelial cells contribute to inflammation and leukocyte infiltration, serving as early markers of renal injury.

Macrophages are a predominant component of tubulointerstitial inflammation in nephrosclerosis (3-5,7). They can differentiate into M1 or M2 phenotypes depending on the microenvironment. M1 macrophages exhibit pro-inflammatory activity, while M2 macrophages have an anti-inflammatory orientation but also contribute to fibrosis by producing profibrotic factors (44-46). The transition from M1 to M2 phenotype occurs as inflammation progresses. Activated macrophages infiltrate the kidney interstitium, sustaining inflammation by releasing pro-inflammatory and profibrotic cytokines (46,47). The production of macrophages is regulated by endogenous anti-inflammatory compounds such as retinoids and (iNOS) Inos (7,20,24). Studies have shown that blocking selectin and β2 integrin reduces macrophage infiltration in the obstructed kidney parenchyma (7,48, 49).

IL-34 produced by tubulointerstitial epithelial cells exacerbates macrophage infiltration in persistent ischemic acute kidney injury, contributing to tubulointerstitial fibrosis. Colony-stimulating factor 1 (CSF-1) expression may aid kidney recovery by restoring renal macrophage polarity. Obstructive uropathy leads to hydrostatic injury in the kidneys, causing mechanical damage to tubular cells and resulting in cell death through necrosis, apoptosis, and autophagy, primarily at the glomerulotubular junction (5,48). Apoptosis affects various renal cell types, leading to the loss of peritubular capillaries, destruction of glomerulotubular junctions, and the formation of atubular glomeruli. Increased tubular apoptosis is associated with tubular atrophy and decreased glomerular filtration rate (3,5,7,12). Apoptosis in tubular cells is stimulated by factors such as TGF-β1, TNF-α, Fas-L, p53, caspases, and ceramide, released by tubular cells and infiltrating macrophages. Suppression of tubular apoptosis is mediated by iNOS, EGF, and IGF-1. Experimental studies have shown that inhibition of EGF, NO, and VEGF exacerbates kidney damage (5,6).

Proximal tubules make up a significant portion of normal kidney volume, and their growth during the perinatal period exceeds that of glomeruli (4). The decrease in proximal tubule mass is associated with nephron heterogeneity, including atrophied nephrons and nephrons undergoing adaptive hypertrophy, which contributes to tubulointerstitial fibrosis (3,4). This can occur due to genetic factors or age-related changes. In cases of adaptive hypertrophy, GFR may remain normal, while albuminuria indicates reduced nephron number (5). Tubulointerstitial fibrosis occurs as a result of ongoing urinary obstruction, leading to inflammatory macrophage infiltration, tubular destruction, and apoptosis. Excessive accumulation of connective tissue in the kidney leads to tubulointerstitial fibrosis, characterized by increased synthesis and deposition of extracellular matrix (ECM). Fibrosis represents a pathological progression of the normal wound healing process, involving injury, inflammation, myofibroblast activation, and ECM deposition and remodelling (3,12).

While the significance of deposited extracellular

matrix (ECM) around damaged tubules is not always considered harmful and may serve to separate intact nephrons from progressive damage, in chronic kidney damage such as CKD, ECM deposition continues and disrupts the kidney's histoarchitecture and function (3). This leads to end-stage renal disease. Similar pathophysiological principles are observed in other fibrotic diseases like liver cirrhosis, cardiomyopathies, and idiopathic pulmonary fibrosis. ECM deposition occurs between the tubular basement membrane and peritubular capillaries, mainly composed of collagen types I, III, V, VI, VII, XV, and the adhesive glycoprotein fibronectin. Elastin and fibrillin also contribute to the fibrotic process (50,51).

During ongoing urinary obstruction, damaged proximal tubule epithelial cells (PTECs) produce pro-inflammatory and profibrotic factors, initiating and sustaining fibrotic processes. This leads to changes in PTEC cytoskeleton, fibroblast proliferation, and transformation into myofibroblasts. The altered microenvironment promotes phenotypic changes in mesenchymal cells and helps PTECs adapt to avoid apoptosis (3).

Tubular epithelial cells (TECs) contribute to kidney fibrosis through a process called epithelial-mesenchymal transition (EMT). During EMT, TECs lose their epithelial characteristics and acquire mesenchymal features. They express mesenchymal markers, migrate into the interstitium, and transform into myofibroblasts, which are cells involved in fibrosis (3).

Myofibroblasts are reactive cells that secrete matrix proteins and play a role in fibrosis. Transforming growth factor beta-1 (TGF-β1) is a key regulator of myofibroblast differentiation (52). Alpha-smooth muscle actin (α-SMA) is a marker for myofibroblasts and is involved in the formation of stress fibers, which connect myofibroblasts to the extracellular matrix. Myofibroblasts also express other markers such as fibronectin, vimentin, and collagen-1α1. The beta receptor of platelet-derived growth factor (PDGFR-β) is expressed by myofibroblasts, fibroblasts, and pericytes (53). The exact contribution of different cell types to the overall matrix mass in renal fibrosis is still not fully understood.

The contribution of EMT to kidney fibrosis is still a topic of debate. Recent studies propose that TECs may undergo partial EMT during fibrosis, expressing markers of both epithelial and mesenchymal cells. However, conclusive evidence of partial EMT in human chronic kidney disease is lacking. While it was previously believed that EMT of TECs was the primary source of myofibroblasts, subsequent studies have questioned this theory. It is now suggested that myofibroblasts may originate from resident interstitial fibroblasts or pericytes. Genetic labeling experiments have shown that endothelial cells and Gli1+ perivascular cells contribute significantly to the myofibroblast population in renal fibrosis. According to LeBleu et al., 50% of myofibroblasts in kidney fibrosis arise from local resident fibroblasts, 35% originate from bone marrow, 10% result from endothelial-to-mesenchymal transition, and 5% result from epithelial-to-mesenchymal transition (56). These findings highlight the complexity of myofibroblast origins and the involvement of various cell types (12,54,55).

Selective tubular injury can trigger inflammation, capillary rarefaction, and fibrosis, indicating the crucial role of damaged tubules in the progression from acute kidney injury (AKI) to CKD. Incomplete recovery after AKI can lead to CKD progression, and abnormal repair processes may result in atrophic or fibrotic phenotypes of tubular epithelial cells. Cell cycle arrest at different phases, such as G2/M or G1/S, may contribute to tubulointerstitial fibrosis through various mechanisms involving signaling pathways and cytokine production (3, 5, 12, 13).

In summary, the understanding of the cellular mechanisms underlying kidney fibrosis is still evolving, and further research is needed to elucidate the precise contributions of different cell types and processes involved in the development and progression of fibrosis.

Discussion

Comprehensive knowledge of the pathogenesis of renal damage in obstructive uropathies allows a more targeted approach to therapeutic interventions. This may involve interventions aimed at relieving the obstruction and restoring normal urine flow, reducing the impact of secondary changes on renal tissue, and promoting the regeneration and recovery of damaged nephrons. Understanding the specific stages of nephropathy formation also opens up the possibility of implementing interventions during the antenatal period, where appropriate, to prevent or minimize the long-term consequences of obstructive uropathies on kidney development (57,58).

One of the key areas of debate revolves around the contribution of EMT to fibrosis. While previous beliefs suggested that EMT of TECs played a significant role in the generation of myofibroblasts, recent studies have challenged this notion. Genetic lineage tracing experiments have failed to provide convincing evidence of direct contribution of TECs to the myofibroblast population (5). However, there are indications of partial EMT, where TECs express both epithelial and mesenchymal markers. This partial EMT may be driven by deletions of EMT transcriptional regulators in TECs, leading to cell cycle arrest and release of fibrogenic cytokines. The origin of myofibroblasts in renal fibrosis is still a matter of discussion. While it was previously believed that TECs undergoing EMT were the primary source, recent studies propose that myofibroblasts may originate from resident interstitial fibroblasts, perivascular cells, or even bone marrow-derived cells. This highlights the complexity and heterogeneity of myofibroblast origins in kidney fibrosis (56).

Understanding the specific contributions of different cell types to the overall pool of myofibroblasts is crucial. Endothelial cells and Gli1+ perivascular cells have been shown to contribute significantly to the myofibroblast population in renal fibrosis. The interplay between different cell types, signaling pathways, and cytokine production remains an active area of research fibrosis (57,58). Incomplete recovery after acute kidney injury (AKI) can lead to fibrotic phenotypes of tubular epithelial cells, contributing to the development and progression of CKD. The involvement of cell cycle arrest at different phases and its impact on tubulointerstitial fibrosis further emphasizes the multifaceted nature of fibrotic processes.

Currently, the discussion of therapeutic strategies for obstructive uropathy mainly focuses on surgical options and techniques aimed at urinary tract drainage and reduction of intracavitary pressure in the kidneys (59-62). In cases of hydronephrosis resulting from obstruction of the ureteropelvic junction, effective surgical methods include ureteroplasty, ureterotomy, bougienage, balloon dilation, and ureteral stenting (61-64). The primary damaging mechanism to the kidney is the increase in intraluminal pressure, which is the main target of therapeutic interventions in clinical practice, including pediatric urology practice. The indications and timing of surgical intervention are still controversial, and even if surgical relief is performed in utero, it may not prevent progressive loss of renal function. Prolonged UUO leads to fibrosis of the renal parenchyma, and even its resolution is accompanied by ongoing kidney damage, while the elimination of ureteral obstruction in experiment within 24 hours was almost fully reversible (65).

There is an urgent need to understand the cellular and molecular mechanisms involved in kidney recovery and develop new treatment methods to prevent end-stage renal failure in these infants and children (13). Inhibiting renal fibrosis is a major direction of experimental research to prevent the progression of CKD. Currently, various therapeutic strategies have been tested in animal studies, demonstrating a reduction in renal fibrosis and restoration of kidney function after relief of ureteral obstruction (66). Active development of treatment strategies is underway, targeting the inhibition of fibrotic and inflammatory proteins, factors inhibiting the activation of the renin-angiotensin system, oxidative stress, prevention of epithelial-to-mesenchymal transition, and suppression of fibroblast proliferation. A promising target for antifibrotic therapy is the mononuclear phagocyte system (66). Currently, four main macrophage-oriented therapeutic strategies are being developed: 1) reducing monocyte and macrophage recruitment to kidney tissue through monocyte pool depletion; 2) blocking macrophage signaling pathways; 3) blocking inflammatory mediators produced by macrophages; 4) reprogramming macrophages through genotype modification or phenotype alteration while maintaining the original genotype, aiming to significantly reduce kidney damage in various nephropathies and improve prognosis (67).

MSCs have emerged as a new treatment modality for kidney disease. MSCs are considered promising cells for cell therapy due to their ease of isolation, low immunogenicity, high proliferative activity, self-renewal and differentiation potential, in vitro expansion capacity, and multidirectional potential due to their anti-inflammatory, anti-apoptotic, angiogenic, antifibrotic, antioxidant effects, as well as their ability to stimulate angiogenesis, regulate autophagy, and aging (67). The main therapeutic effects of MSCs are mediated by extracellular vesicles derived from MSCs (MSC-EVs), which carry molecules such as VEGF, HGF, IGF-1, IL-10, fibroblast growth factor (FGF), and TGF-α. MSC-EVs suppress the inducibility of related pro-

inflammatory molecules (such as IL-1β and TNF-α), thereby exerting anti-inflammatory and anti-apoptotic effects and promoting kidney restoration (68).

Anti-fibrotic effects of numerous pharmacological agents have been studied on the UUO model, including nonsteroidal anti-inflammatory drugs, antifibrotic agents, renin-angiotensin system antagonists, endothelin A/B receptor blockers, Chinese medicine, as well as allopurinol, L-arginine, bone morphogenetic protein-7, epidermal growth factor, etc. (65,69-72).

Conclusions

These emerging modalities have shown therapeutic potential in attenuating renal damage and promoting tissue repair, offer exciting prospects for future therapeutic interventions. However, further research and clinical trials are necessary to validate the efficacy and safety of these potential therapeutic targets and strategies. Translating these findings into clinical practice will require a multidisciplinary approach and collaborative efforts among researchers and clinicians.

Conflict of interest:

The authors report no conflict of interest.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Contributions

Research concept and design: **DLA**
Data analysis and interpretation: **DLA, PEB**
Collection and/or assembly of data: **DLA, KEI**
Writing the article: **DLA**
Critical revision of the article: **VVR**
Final approval of the article: **DLA, VVR**

References

1. Papayan AV, Savenkova ND. "Clinical Nephrology in Childhood" published in St. Petersburg by "SOTIS" in 1997, pp: 718.
2. Ingelfiger JR, Kalantar-Zadeh K, Schaefer F. Averting the legacy of kidney disease—Focus on childhood. Saudi J Kidney Dis Transpl. 2016;27:219-26.
3. Humphreys BD. Mechanisms of Renal Fibrosis. Ann Rev Physiol. 2018;80:6.1-6.18.
4. Chevalier RL. Congenital urinary tract obstruction: the long view. Adv Chronic Kidney Dis. 2015;22(4):312-9.
5. Chevalier RL. The proximal tubule is the primary target of injury and progression of kidney disease: role of the glomerulotubular junction. Am J Physiol Renal Physiol. 2016;311:F145-F161.
6. Martínez-Klimova E, Aparicio-Trejo OE, Tapia E, Pedraza-Chaverri J. Unilateral Ureteral Obstruction as a Model to Investigate Fibrosis-Attenuating Treatments. Biomolecules. 2019;9(4):141.
7. Jackson L, Woodward M, Coward RJ. The molecular biology of pelvi-ureteric junction obstruction. Pediatr Nephrol. 2018;33(4):553-71.
8. Bagińska J, Korzeniecka-Kozerska A. Are Tubular Injury Markers NGAL and KIM-1 Useful in Pediatric Neurogenic Bladder? J Clin Med. 2021;10:2353.
9. Pope JC. Showalter PR, Milam DF, Brock JW. Intrapelvic pressure monitoring in the partially obstructed porcine kidney. Urology. 1994;44:565-71.
10. Holden D, George NJ, Rickards D, Barnard RJ, O'Reilly PH. Renal pelvic pressures in human chronic obstructive uropathy. Br J Urol. 1984;56:565-70.
11. Madsen MG. Urinary biomarkers in hydronephrosis. Dan Med J. 2013;60:B4582.
12. Bi-Cheng Liu, Tao-Tao Tang, Lin-Li Lv, Hui-Yao Lan. Renal tubule injury: a driving force toward chronic kidney disease. Kidney Int. 2018;93(3):568–79.
13. Nagalakshmi VK, Li M, Shah S, Gigliotti JC, Klibanov AL, Epstein FH, et al. Changes in cell fate determine the

regenerative and functional capacity of the developing kidney before and after release of obstruction. Clin Sci (Lond). 2018;132(23):2519-45.

14. Chevalier RL, Kim A, Thornhill BA, Wolstenholme JT. Recovery following relief of unilateral ureteral obstruction in the neonatal rat. Kidney Int. 1999;55(3):793-807.

15. Thornhill BA, Forbes MS, Marcinko ES, Chevalier RL. Glomerulotubular disconnection in neonatal mice after relief of partial ureteral obstruction. Kidney Int. 2007;72(9):1103-12.

16. Thornhill BA, Burt LE, Chen C, Forbes MS, Chevalier RL. Variable chronic partial ureteral obstruction in the neonatal rat: a new model of ureteropelvic junction obstruction. Kidney Int. 2005;67(1):42-52.

17. Thornhill BA, Chevalier RL. Variable partial unilateral ureteral obstruction and its release in the neonatal and adult mouse. Methods Mol Biol. 2012;886:381-92.

18. Chevalier RL. Chronic partial ureteral obstruction and the developing kidney. Pediatr Radiol. 2008;38(1):S35-40.

19. Chevalier RL, Forbes MS, Thornhill BA. Ureteral obstruction as a model of renal interstitial fibrosis and obstructive nephropathy. Kidney Int. 2009;75:1145-52.

20. Chevalier RL, Thornhill BA, Forbes MS, Kiley SC. Mechanisms of renal injury and progression of renal disease in congenital obstructive nephropathy. Pediatr Nephrol. 2010;25(4):687-97.

21. Madsen MG, Nørregaard R, Frøkiær J, Jørgensen TM. Urinary biomarkers in prenatally diagnosed unilateral hydronephrosis. J Pediatr Urol. 2011;7(2):105-12.

22. Madsen MG, Nørregaard R, Stødkilde L, Christensen JH, Jørgensen TM, Frøkiær J. Urine and kidney cytokine profiles in experimental unilateral acute and chronic hydronephrosis. Scand J Urol Nephrol. 2012;46(2):91-6.

23. Liu BC, Tang TT, Lv LL. How Tubular Epithelial Cell Injury Contributes to Renal Fibrosis. Adv Exp Med Biol. 2019;1165:233-252.

24. Klein J, Gonzalez J, Miravete M, Caubet C, Chaaya R, Decramer S, et al. Congenital ureteropelvic junction obstruction: human disease and animal models. Int J Exp Pathol. 2011;92:168-92.

25. Chevalier RL. Obstructive nephropathy: towards biomarker discovery and gene therapy. Nat Clin Pract Nephrol 2006;2:157-68.

26. Frokiaer J, Knudsen L, Nielsen AS, Pedersen EB, Djurhuus JC. Enhanced intrarenal angiotensin II generation in response to obstruction of the pig ureter. Am J Physiol 1992;263:F527-F533.

27. Hammad F.T. The long-term renal effects of short periods of unilateral ureteral obstruction Int J Physiol Pathophysiol Pharmacol. 2022;14(2):60-72.

28. Moody TE, Vaughn ED Jr, Gillenwater JY. Relationship between renal blood flow and ureteral pressure during 18 hours of total unilateral uretheral occlusion. Implications for changing sites of increased renal resistance. Invest Urol. 1975;13:246-51.

29. Cadnapaphornchai P, Aisenbrey G, McDonald KM, Burke TJ, Schrier RW. Prostaglandin-mediated hyperemia and renin-mediated hypertension during acute ureteral obstruction. Prostaglandins. 1978;16:965-71.

30. Aranda-Rivera AK, Cruz-Gregorio A, Aparicio-Trejo OE, Ortega-Lozano AJ, Pedraza-Chaverri J. Redox signaling pathways in unilateral ureteral obstruction (UUO)-induced renal fibrosis. Free Radic Biol Med. 2021;172:65-81.

31. Martínez-Klimova E, Aparicio-Trejo OE, Go´mez-Sierra T, Jim´enez-Uribe AP, Bellido B, Pedraza-Chaverri J. Mitochondrial dysfunction and endoplasmic reticulum stress in the promotion of fibrosis in obstructive nephropathy induced by unilateral ureteral obstruction. Biofactors. 2020;46(5):716-33.

32. Bhargava P, Schnellmann RG. Mitochondrial energetics in the kidney. Nat Rev Nephrol. 2017;13(10):629-46.

33. Chen J, Li D. Telbivudine attenuates UUO-induced renal fibrosis via TGF-β/Smad and NF-κB signaling. Int Immunopharmacol. 2018;55:1-8.

34. Fern RJ, Yesko CM, Thornhill BA, Kim HS, Smithies O, Chevalier RL. Reduced angiotensinogen expression attenuates renal interstitial fibrosis in obstructive nephropathy in mice. J Clin Invest. 1999;103(1):39-46.

35. Shen Y, Miao NJ, Xu JL, Gan XX, Xu D, Zhou L, et al. N-acetylcysteine alleviates angiotensin II-mediated renal fibrosis in mouse obstructed kidneys. Acta Pharmacol Sin. 2016;37(5):637-44.

36. Wang W, Huang XR, Canlas E, Oka K, Truong LD, Deng C, et al. Essential role of Smad3 in angiotensin II-induced vascular fibrosis. Circ Res. 2006;98(8):1032-9.

37. Nakatani T, Tamada S, Asai T, Iwai Y, Kim T, Tsujino T, et al. Role of renin-angiotensin system and nuclear factor-κb in the obstructed kidney of rats with unilateral ureteral obstruction. Jpn J Pharmacol. 2002;90:361-4.

38. Grande MT, Pérez-Barriocanal F, López-Novoa JM. Role of inflammation in túbulo-interstitial damage associated to obstructive nephropathy. J Inflamm. 2010;7:19.

39. Esteban V, Lorenzo O, Rupe´rez M, Suzuki Y, Mezzano S, Blanco J, et al. Angiotensin II, via AT1 and AT2 receptors and NF-kappaB pathway, regulates the inflammatory response in unilateral ureteral obstruction. J Am Soc Nephrol. 2004;15:1514-29.

40. Aparicio-Trejo OE, Tapia E, Sánchez-Lozada LG, Pedraza-Chaverri J. Mitochondrial bioenergetics, redoX state, dynamics and turnover alterations in renal mass

reduction models of chronic kidney diseases and their possible implications in the progression of this illness. Pharmacol Res. 2018;135(1):1-11.

41. Bhatia D, Chung KP, Nakahira K, Patino E, Rice MC, Torres LK, et al. Mitophagy-dependent macrophage reprogramming protects against kidney fibrosis. JCI Insight. 2019;4:e132826.

42. Chevalier RL. Molecular and cellular pathophysiology of obstructive nephropathy. Pediatr Nephrol. 1999;13:612-9.

43. Chevalier RL. Prognostic factors and biomarkers of congenital obstructive nephropathy. Pediatr Nephrol. 2016;31:1411-20.

44. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. Immunity. 2014;41(1):14-20.

45. Funes SC, Rios M, Escobar-Vera J, Kalergis AM. Implications of macrophage polarization in autoimmunity. Immunology. 2018;154(2):186-95.

46. Morozova OL, Budnik IA, Morozov DA, Mal'tseva LD, Mel'nikova YuA. Macrophages, a new target for anti-fibrotic therapy in children with obstructive uropathy. Pediatrics. 2015;94(3):182-7.

47. Duffield JS. Macrophages and immunologic inflammation of the kidney. Semin Nephrol. 2010;30(3):234-54.

48. Liu Y, Zou XB, Chai YF, Yao YM. Macrophage polarization in inflammatory diseases. Int J Biol Sci. 2014;10(5):520-9.

49. Lange-Sperandio B, Cachat F, Thornhill BA, Chevalier RL. Selectins mediate macrophage infiltration in obstructive nephropathy in newborn mice. Kidney Int. 2002;61:516-24.

50. Genovese F, Manresa AA, Leeming DJ, Karsdal MA, Boor P. The extracellular matrix in the kidney: a source of novel non-invasive biomarkers of kidney fibrosis? Fibrogenesis Tissue Repair. 2014;7:4.

51. Liu Y. Cellular and molecular mechanisms of renal fibrosis. Nat Rev Nephrol. 2011;7:684-96.

52. Kanzler S, Lohse AW, Keil A, Henninger J, Dienes HP, et al. TGF-β1 in liver fibrosis: an inducible transgenic mouse model to study liver fibrogenesis. Am J Physiol. 1999;276:G1059–G1068.

53. Lin SL, Kisseleva T, Brenner DA, Duffield JS. Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am J Pathol. 2008;173(6):1617-27.

54. Prunotto M, Budd DC, Gabbiani G, Meier M, Formentini I, Hartmann G, Pomposiello S, Moll S. Epithelial-mesenchymal crosstalk alteration in kidney fibrosis. J Pathol. 2012;228(2):131-47.

55. Liu Y. New insights into epithelial-mesenchymal transition in kidney fibrosis. J Am Soc Nephrol. 2010;21(2):212-22.

56. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, et al. Origin and function of myofibroblasts in kidney fibrosis. Nat Med. 2013;19:1047-53.

57. Tammaro A, Kers J, Scantlebery AML, Florquin S. Metabolic Flexibility and Innate Immunity in Renal Ischemia Reperfusion Injury: The Fine Balance Between Adaptive Repair and Tissue Degeneration. Front Immunol. 2020;11:1346.

58. Schelling JR. Tubular atrophy in the pathogenesis of chronic kidney disease progression. Pediatr Nephrol. 2016;31:693-706.

59. Radmayr C, Bogaert G, Dogan HS, Nijman JM, Rawashdeh YFH, Silay MS, et al. EAU Guidelines on Pediatric Urology. In: European Association of Urology (online). Uroweb, 2021 (vid. 2021-02-24). Available from: https://uroweb.org/guideline/paediatric-urology/

60. Onen A. Grading of Hydronephrosis: An Ongoing Challenge. Front Pediatr. 2020;8:458.

61. Nguyen HT, Herndon CD, Cooper C, Gatti J, Kirsch A, Kokorowski P, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol. 2010;6(3):212-31.

62. Nordenström J, Koutozi G, Holmdahl G, Abrahamsson K, Sixt R, Sjöström S. Changes in differential renal function after pyeloplasty in infants and children. J Pediatr Urol. 2020;16(3):329.e1-329.e8.

63. Meng C, Gan L, Li K, Peng L, Li J, Yang J, et al. Comparison of external stents and DJ stents techniques for pediatric pyeloplasty: A systematic review and meta-analysis. Front Pediatr. 2022;10:933845.

64. Kaeidi A, Maleki M, Shamsizadeh A, Fatemi I, Hakimizadeh E, Hassanshahi J. The therapeutic approaches of renal recovery after relief of the unilateral ureteral obstruction: A comprehensive review. Iran J Basic Med Sci. 2020;23(11):1367-73.

65. Martínez-Klimova E, Aparicio-Trejo OE, Tapia E, Pedraza-Chaverri J. Unilateral Ureteral Obstruction as a Model to Investigate Fibrosis-Attenuating Treatments. Biomolecules. 2019;9(4):141.

66. Morozova OL, Budnik IA, Morozov DA, Mal'tseva LD, Mel'nikova YuA. Macrophages, a new target for anti-fibrotic therapy in children with obstructive uropathy. Pediatrics. 2015;94:182-7.

67. Chen F, Chen N, Xia C, Wang H, Shao L, Zhou C, et al. Mesenchymal Stem Cell Therapy in Kidney Diseases: Potential and Challenges. Cell Transplant. 2023;32:1-23.

68. Li JK, Yang C, Su Y, Luo JC, Luo MH, Huang DL, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles: A Potential Therapeutic Strategy for Acute Kidney Injury. Front Immunol. 2021;12:684496.

69. Tan W, Wang Y, Dai H, Deng J, Wu Z, Lin L, et al. Potential Therapeutic Strategies for Renal Fibrosis: Cordyceps and Related Products. Front Pharmacol. 2022;13:932172.

70. Bai X, Nie P, Lou Y, Zhu Y, Jiang S, Li B, et al. Pirfenidone Is a Renal Protective Drug: Mechanisms, Signaling Pathways, and Preclinical Evidence. Eur J Pharmacol. 2021;911:174503.

71. Kianfar T, Kadkhodaee M, Seifi B, Abdia A, Adelipour M, Pishkenari BH, et al. The effect of tannic acid on renal renin-angiotensin signaling pathway in a model of unilateral ureteral obstruction in male Wistar rats. Naunyn Schmiedebergs Arch Pharmacol. 2023. doi: 10.1007/s00210-023-02548-9.

72. Kim S, Kim SJ, Yoon HE, Chung S, Choi BS, Park CW, et al. Fimasartan, a Novel Angiotensin-Receptor Blocker, Protects against Renal Inflammation and Fibrosis in Mice with Unilateral Ureteral Obstruction: the Possible Role of Nrf2. Int J Med Sci. 2015;12(11):891-904.