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Pathophysiological Outcomes of Ureteral Obstruction: An Update

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Abstract

Renal impairment is frequently caused by blockage of the urine flow through urinary tract. Obstructive nephropathy can be induced by either unilateral or bilateral obstruction of ureter. For a long time, obstructive nephropathy was thought to be only a mechanical issue. Recent developments in cell and systems biology, have shown a complex physiopathology including a large number of molecular mediators of injury that contribute to cellular processes such as apoptotic cell death, cell injury, inflammation, and fibrosis. A chronic blockage causes tubular and glomerular obstruction. In addition to the acute impact on glomerular filtration rate and tubule function, interstitial damage also caused by the activation of several pathways. Chronic tubulointerstitial damage develops when tubulointerstitial injury progresses. Tubular atrophy,hypertropy, inflammatory cell infiltration, and interstitial fibrosis are signs of renal injury. Based on current knowledge of the pathophysiology of renal damage, this minireview highlights the emerging events observed in obstructive nephropathy.

Keywords: 1 Ureteral obstruction, 2 Fibrosis,3 Inflammation, 4 Apoptosis, 5 Tubular injury, 6 TGF-β

Introduction

Obstruction in flow of urine in any part of urinary system leads to obstructive nephropathy which can be induced by unilateral or bilateral ureteral obstruction. UUO can be achieved by either reversible or irreversible ligation of ureter. Irreversible UUO is characterised by ureter dilation, reduced renal blood flow, decrease in glomerular filtration rate, increasingly severe renal inflammation and interstitial fibrotic scarring while reversible UUO (R-UUO) is characterised by hydronephrosis, tubular dilation and inflammation[1].

In children, UUO is a frequent cause of end-stage renal disease (ESRD), accounting for 21% of chronic kidney disease (CKD) and for 16% of children listed for transplantation. In adults, UUO is a frequent cause of acute kidney injury (AKI). Up to 17% of AKI are secondary to UUO [2].

Clinically, ureteral obstruction maycause by (a) urolithiasis, (b) congenital urinary tract malformations such as obstructive megaureter, uretero-pelvic junction obstruction, duplicated collecting system, horseshoe kidney, (c) immuno-rheumatologic diseases such as necrotizing vasculitis, periarteritis nodosa, kawasaki disease, henoch-schönlein purpura, eosinophilic ureteritis, (d) ureteral localization of infections like fungal infections, viral infections, bacterial infections,

tubercular infections and (e) neoplastic intrinsic ureteral obstructions such as fibroepithelial polyps, ureteritis cystica, malignant neoplasms [3].

Irreversible ureteral obstruction

Many studies have reported that complete or irreversible ureteral obstruction is achievedby permanently obstruct the ureter by ligation with suture or by application of ligating clip [1, 4-6] and is used to study renal inflammation and fibrosis [7]. It leads to blockage of urine flow thereby increasing hydrostatic pressure towards to kidney which triggers tubular cell death by renal fibrosis, interstitial inflammation, apoptosis and necrosis [8].

The sequence of events initiates rapidly in the kidney obstructed by complete UUO, leads within 24 h to reduced renal bloodflow and glomerular filtration ratefollowed by hydronephrosis, interstitial inflammatory infiltration (macrophages), and tubular cell death which leads to apoptosis and necrosis. Tubular epithelial cell death is caused by a number ofstressors including ischemia, hypoxia and oxidant injury and axial strain caused by tubular dilatation[9].

Reversible ureteral obstruction

Reversible unilateral ureteral obstruction (R-UUO) is prominent model of renal injury and used to study the structural and functional changes such as inflammatory and immune processes, cellular and tissue regeneration in kidneys after relief of the obstruction. R-UUO model is advantageous model to assess kidney recovery after obstructive uropathy because it is a simple, easy, reproducible and more reliable method since it includes the nephrectomy of the contralateral kidney in order to invalidate its compensatory effect. [7].

In R-UUO model, the ureter is ligated for a suitable period of time sufficient to induce hydronephrosis, tubular dilation, inflammation and renal fibrosis. Then the ureteric obstruction is surgically reversed by anastomosis and kidney is allowed to decompress so that urinary flow get restored toward the bladder. Due to this obstructed kidney which got hydronephrotic due to obstruction in urine flow becomes normal [1]. As a result, this model provides opportunity to investigators to explore the resolution of kidney inflammation together with key aspects of tissue repair [10].

Events involved in pathophysiological changes in UUO

Large number of studies has been performed to recognize the cellular and molecular effects obtained after ureteral obstruction [11]. Obstruction in ureter leads to changes in hydrostatic pressures, glomerular filtration, renal hemodynamics, and tubular function has been described well previously [12]. Apart from this various cellular event which includes tubular dilation, phenotypic cellular transition, interstitial inflammation, followed by glomerulotubular injury and progressive interstitial fibrosis also found.

Tubular Injury

Tubular injury had occurred due to partial expansion in renal tubular lumen, degeneration of renal tubular epithelial cells which leads to tubular dilation [7].Additionally, obstructionalso rises hydrostatic pressure which got transmitted back and eventually decreases the glomerular filtration rate (GFR) [12].Moreover, obstructed kidney undergoes hydronephrotic with loss of brush border cells, tube formation with narrowing of renal parenchyma. In previous study in genetically modified $\beta^{6-/-}$ mice model, tubular injury was found in 5 days in wild type mice which get proceeded in 14 days in renal cortex and medulla but significantly get decreased in knockout mice[13].

Tubular Apoptosis

Apoptosis is a type of energy-dependent cell death that is brought on by harmful stimuli or a lack of survival factors. In UUO, tubular atrophy is caused by an increased rate of tubular cell death, with additional processes such as epithelial-mesenchymal transition playing a role (EMT) [14]. In UUO, apoptosis is observed in tubules as well as in interstitial cells in time dependent manner. Apoptosis in tubules is observed just a day after UUO induction whereas in interstitial cells it found to be after 3 days [15]. Moreover, we found that Ang-II, TGF-β1, members of the TNF cytokine superfamily, oxidative stress, ATP depletion and mechanical stretchare also major triggerer of tubular apoptosis in UUO [16]

Tubular Fibrosis

Fibrosis is well defined characteristic feature observed in ureteral obstruction. In fibrosis, there is rise numbers of activated fibroblasts and also various extracellular matrix components such as collagen I, III, and IV, proteoglycans, fibronectin gets accumulated [17]. It was reported that there is presence of α-SMA as well as expression of collagen-1 in tubulointerstitial space indicates the presence of interstitial myofibroblasts [7, 18]. Apart from that tubular fibrosis in obstructed nephropathy induced by UUO also promoted by mitochondrial dysfunction and endoplasmic reticulum stress [13]. Fibrotic processes have been related to mitochondrial impairment also promotes kidney function deterioration in obstructive nephropathy [19-21]. Another study reported that breakdown of epithelial junctions and consequent loss of cell polarity are hallmarks of EMT [22].

Tubulointerstitial Inflammation

Inflammation is a complicated event that reflects local and/or systemic reactions to many stresses, and it typically allows disease resistance, tissue repair, and normal function restoration with the least amount of tissue damage feasible. Due to reversible obstruction in ureter, tubules get injured and initiate the secretion of macrophages, CD40, pro-inflammatory cytokines IL-2, MCP-1 and iNOS and also pro-fibrotic cytokine TGF-β1 [7].In previous study it was observed that interstitial inflammation due to infiltration of interstitial cells progressively enhanced from 12 hours after obstruction to upto 14 days [23,24]. A significant increase of adhesion molecules (ICAM-1 and VCAM-1), monocyte chemoattractive protein (MCP-1) and the glycoprotein osteopontin (OPN) is found after a few hours of ureteral blockage[23,25,26].The increased expression of these molecules lasts for 7–10 days after the blockage has been removed. Within 5 days following blockage, ICAM-1 and OPN appear to have a function, although MCP-1 and VCAM-1 gene induction continues to rise [26-28].

Conclusion

In this review author try to convey about UUO and physiological and pathophysiological events occurs in tubules and kidney. Ureteral obstruction leads to tubular injury, apoptosis inflammation and fibrosis.

Consent for publication

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Declaration of Competing Interest

The authors declare that they have no potential conflicts of interest related to the contents of this article.

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