Obstructive Nephropathy

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Abstract

Obstructive nephropathy is a relatively common entity that is treatable and often reversible. It occurs at all ages from infancy to elderly subjects. Obstructive uropathy is classified according to the degree, duration and site of the obstruction. It is the result of functional or anatomic lesions located in the urinary tract. The causes of obstructive uropathy are many. Obstruction of the urinary tract may decrease renal blood flow and the glomerular filtration rate. Several abnormalities in tubular function may occur in obstructive nephropathy. These include decreased reabsorption of solutes and water, inability to concentrate the urine and impaired excretion of hydrogen and potassium. Renal interstitial fibrosis is a common finding in patients with long-term obstructive uropathy. Several factors: macrophages, growth factors, hypoxia, cytokines are involved in the pathogenesis of interstitial fibrosis. It has been shown that ACE inhibitors ameliorate the interstitial fibrosis in animals with obstructive uropathy. (Internal Medicine 39: 355–361, 2000)

Key words: angiotensin II, acute renal failure, interstitial fibrosis

Introduction

Obstructive nephropathy is of great importance to clinicians because it is a common entity that is treatable and often reversible. Patients with obstructive nephropathy may be asymptomatic or may exhibit a diversity of clinical syndromes (see Table 1). Obstructive uropathy refers to the presence of structural or functional changes in the urinary tract that impede the normal flow of urine. Obstructive nephropathy is the renal disease caused by impaired flow of urine or tubular fluid. Hydronephrosis denotes dilation of the urinary tract.

Incidence and Prevalence of Obstructive Uropathy

Obstructive uropathy is a common entity that occurs at all

ages. The incidence of hydronephrosis reported by Bell (1) in a series of 32,360 autopsies was 3.8% (3.9% in males, 3.6% in females). The incidence of clinical manifestations of obstructive uropathy prior to death was not reported, and it is likely that hydronephrosis was an incidental finding in many of these patients. The incidence of hydronephrosis at autopsy is somewhat lower in children than in adults, being 2% in one series of 16,100 autopsies (2). Over 80% of children with hydronephrosis at autopsy were less than 1 year old, with the balance of childhood cases being distributed uniformly through the childhood years. About 166 patients per 100,000 population had a presumptive diagnosis of obstructive uropathy on admission to hospitals in the United States in 1985 (3). Among male patients with kidney and urologic disorders, obstructive uropathy ranked fourth at discharge (242 patients/100,000 discharges). In females with kidney and urologic disorders, obstructive uropathy ranked sixth as a diagnosis at discharge (94 patients/100,000 discharges). In the United States in 1985, about 387 visits per 100,000 population were related to obstructive uropathy (3). New ultrasound techniques have made possible the diagnosis of obstructive uropathy in the fetus during pregnancy (4, 5). In the adult, the incidence and causes of urinary tract obstruction vary with the age and sex of the patient. In young and middle-aged males, acute obstruction from renal calculi is common but temporary, and such cases would not be included in autopsy surveys. In females of this age group, on the other hand, pelvic cancer is an important cause of obstructive uropathy. In the older age group, urinary tract obstruction is more common in the male, resulting from prostatic hypertrophy or malignancy.

In 1985, about 80% of the operations for benign prostatic hyperplasia were performed on men age 65 years or older. From 1989 to 1993, a 5-year span, 4,869 patients with the diagnosis of obstructive nephropathy began treatment for end-stage renal disease (ESRD) in the United States (3). During this period, obstructive nephropathy accounted for 2% of the patients being treated under Medicare regulations for ESRD. Among the 4,869 patients with obstructive nephropathy being treated for ESRD, 6.9% were younger than 20 years of age, 35.7% were between the ages of 20 and 64 and 57.4% were older than 64 years. Males comprised 73.8% of patients with obstructive nephropathy being treated with ESRD.

Table 1. Clinical Presentation of Obstructive Nephropathy

Presentation	Cause
Acute renal failure	Complete bilateral obstruction (or complete obstruction of a solitary kidney)
Chronic renal failure	Severe partial bilateral obstruction
Flank pain and/or enlarged, tender kidney	Unilateral obstruction partial or complete
Polyuria, polydipsia, sodium wasting, and/or renal tubular acidosis	Chronic partial obstruction or post-obstructive diuresis
Hypertension	Increased ECF volume (bilateral obstruction): increased renin-angiotensin (unilateral obstruction)
Polycythemia	Increased renal production of erythropoietin (presumably due to renal ischemia during obstruction)
Bladder Symptoms: hesitancy, incontinence, decreased caliber of urine stream	Obstruction of lower urinary tract (bladder neck, bladder pathology)
Repeated or refractory urinary tract infections	Any obstructive lesion but most commonly lower urinary tract

Classification and Pathogenesis

Anatomic or functional factors are important in establishing the cause of the obstruction. The level at which the obstruction occurs in the urinary tract, and whether it is intraluminal, intramural (intrinsic), or extramural (extrinsic) are helpful. The important levels of obstruction in the urinary tract are the urethra and the bladder neck, the bladder and the ureterovesical junction, the ureter, and the renal pelvis and ureteropelvic junction.

Obstructive uropathy is classified according to the degree, duration, and site of the obstruction. The degrees of obstruction are said to be high grade when it is complete, and low grade when partial or incomplete. When the obstruction is of short duration it is said to be acute. Most often this is due to stones. Obstruction that develops slowly and is long lasting is said to be chronic, as in congenital ureterovesical abnormalities and retroperitoneal fibrosis. Obstructive uropathy is due to functional or anatomic lesions that can be located anywhere in the urinary tract from the renal tubules (crystals) to the urethral meatus. Obstructive uropathy affecting the lumen of the renal tubules is said to be intrarenal, and those causes of obstruction that arise in the urinary tract are referred to as extrarenal. Extrarenal obstruction in turn is divided into upper urinary tract obstruction (above the ureterovesical junction), which is usually unilateral in nature, and lower urinary tract obstruction, which by definition is bilateral.

The causes of upper urinary tract obstruction can be intrinsic or extrinsic. Intrinsic causes are either intraluminal or intramural, with renal calculi being the main cause of intraluminal obstruction. The intramural causes of obstruction are either anatomic or functional. Anatomic lesions of the upper urinary tract, a less common cause of obstruction, include ureteral strictures, benign or malignant tumors of the renal pelvis and ureter, ureteral valves and polyps. The functional disorders include vesicoureteral reflux and adynamic ureteral segments. The most common site of functional obstruction in the ureters is a functional defect at the ureteropelvic junction. This is usually a disease of infants. The second most common cause is a functional defect at the ureterovesical junction. This is a disease primarily of male children. The extrinsic causes of obstructive uropathy are best classified under the system of origin of the obstructing lesion. The lesions causing obstruction may originate in the reproductive system, the vascular system, the gastrointestinal tract, or the retroperitoneal space (see Table 2).

The causes of lower urinary tract obstruction include lesions of the urethra, prostate, and bladder. Anatomical or functional abnormalities of the bladder may result in obstruction. Urethral strictures usually result from chronic instrumentation or gonococcal infections. In males, benign prostatic hyperplasia and prostatic cancer, particularly in the elderly, are major causes of lower urinary tract obstruction.

Table 2. Causes of Urinary Tract Obstruction

Upper urinary tract	Lower urinary tract
Intrinsic causes <ol style="list-style-type: none"> 1. Intraluminal <ol style="list-style-type: none"> 1. Intratubular deposition of crystals (uric acid) 2. Ureter: urolithiasis, blood clots, papillary tissue 2. Intramural <ol style="list-style-type: none"> 1. Dysfunction at the ureteropelvic or ureterovesical junction 2. Ureteral valve, polyp, or stricture 	<ol style="list-style-type: none"> 1. Phimosi, meatal stenosis, paraphimosis 2. Urethra: strictures, stones, diverticulum, posterior or anterior ureteral valves, periurethral abscess, urethral surgery 3. Prostate: benign prostatic hyperplasia, prostatic calculi, abscess, prostatic carcinoma 4. Bladder <ol style="list-style-type: none"> a. Neurogenic bladder: spinal cord defect or trauma, diabetes, multiple sclerosis, cerebrovascular accidents, Parkinson's disease b. Bladder neck dysfunction c. Bladder calculus d. Bladder cancer 5. Trauma <ol style="list-style-type: none"> a. Straddle injury b. Pelvic fracture
Extrinsic causes <ol style="list-style-type: none"> 1. Reproductive system <ol style="list-style-type: none"> a. Uterus: pregnancy, prolapse, tumors, endometriosis b. Ovary: abscess, tumors, ovarian remnants c. Gartner's duct cyst, tuboovarian abscess 2. Vascular lesions <ol style="list-style-type: none"> a. Aneurysm: abdominal aorta, iliac vessels b. Aberrant vessels: ureteropelvic junction c. Venous: retrocaval ureter, ovarian vein thrombophlebitis d. Fibrosis following vascular reconstructive surgery 3. Gastrointestinal tract: Crohn's disease, diverticulitis, appendiceal abscess, tumors, pancreatic tumors, abscess, cysts 4. Diseases of the retroperitoneum <ol style="list-style-type: none"> a. Retroperitoneal fibrosis (idiopathic, radiation) b. Inflammatory: tuberculosis, sarcoidosis c. Hematomas d. Primary retroperitoneal tumors (lymphoma, sarcoid, etc.) e. Tumor metastatic to the retroperitoneum (cervix, bladder, colon, prostate, etc.) f. Lymphocele g. Pelvic lipomatosis 	

Blood Flow, Glomerular and Tubular Function in Obstructive Nephropathy

In experimental animals, acute ureteral obstruction causes a transient increase in blood flow to the affected kidney, followed by progressive vasoconstriction. Local production of eicosanoids, especially prostacyclin and prostaglandin E may account for the increased renal blood flow observed after the onset of obstruction. Usually 3 to 5 hours after the onset of the obstruction there is an increase in intrarenal resistance. This vasoconstriction is mediated by several vasoactive compounds such as angiotensin II, (6) thromboxane A₂ (7) and antidiuretic hormone (8). In addition, decreased production of nitric oxide may also have a role in the increase in vascular resistance.

Glomerular filtration rate (GFR) declines progressively after the onset of complete ureteral obstruction. There is an increase in pressure in the proximal tubule. This results in a de-

crease in the net hydraulic pressure gradient across glomerular capillaries, resulting in a decline in GFR. The decrease in whole kidney GFR after ureteral ligation is due to both a decrease in single nephron GFR and a decrease in the number of filtering nephrons.

Several abnormalities in tubular function may occur in obstructive nephropathy. Some of the abnormalities include: decreased reabsorption of solutes and water, inability to concentrate the urine, impaired excretion of hydrogen and potassium. Impaired ability to concentrate the urine is evident after relief of obstruction in both animals and human subjects. Vasopressin administration does not correct the defect (9, 10). A decrease in the solute content of the papillary interstitium may be a major factor underlying this abnormality. A decreased expression of aquaporins in the distal tubule may be also a contributory factor.

The fractional excretion of potassium is decreased in patients with obstructive uropathy. Thus, patients with this disorder

der may develop hyperkalemic/hyperchloremic acidosis, particularly those with chronic obstruction (11). An inability to acidify the urine is seen after release of obstruction in both humans and experimental animals (12–16). Although this acidifying defect is reversible in most instances, it may persist in some patients (12). In animals with ureteral obstruction, there is a decreased number of H⁺-ATPase pumps in the apical surface of intercalated cells. This event may account for the acidifying defect seen after release of ureteral obstruction (17).

Mechanisms of Interstitial Fibrosis in Obstructive Nephropathy

Interstitial fibrosis is a common finding in the kidney with long-term ureteral obstruction (18). The process of fibrosis, in part, represents an imbalance between extracellular matrix protein synthesis and degradation. An early event in the interstitial fibrosis process is the infiltration of the tubulointerstitial

compartment by macrophages (19). Since the macrophage is a rich source of numerous peptide growth factors, it is not unexpected that such compounds have a pivotal role in initiating and maintaining the fibrogenesis of the tubulointerstitium. Also, the cortical tubular cells in the kidney are capable of elaborating a number of peptide growth factors in response to the mechanical perturbation that occurs after ureteral obstruction (18). Macrophages and renal tubular cells are a source of a number of growth factors and inflammatory agents such as, interleukin 1 and interleukin 6, transforming growth factor β (TGF- β), tumor necrosis factor (TNF), platelet-derived growth factor (PDGF) and fibroblast growth factor (PGF).

The deposition and accumulation of extracellular matrix (ECM) following tubulo-interstitial injury represents an imbalance between deposition and removal of collagen and other compounds. There is a down-regulation of proteases which degrade matrix components. On the other hand, the upregulation of TGF- β results in a variety of cellular responses that promote fibrosis, including stimulation of ECM genes, down regulation of degradative matrix metalloproteinases and up-regulation of tissue inhibitor of metalloproteinase (TIMP) 1 (20, 21).

Recent studies have suggested that tension stress (22), hypoxia (23), macrophage infiltration (24), and increased production of cytokines (25–27) may affect the redox state *in vitro*. To investigate the potential role of oxidative stress, Kawada et al (28) examined the levels of distribution of N^G carboxymethyl-lysine (CML) in the kidney with ureteral obstruction. They found CML in the interstitium of the obstructed kidney 10 days after ligation of the ureter. Heme oxygenase mRNA was upregulated 12 hours after ureteral obstruction. These results indicate the presence of oxidative stress in the interstitium of the obstructed kidney. Oxidative stress and the production of several active oxidative products may play an important role in interstitial inflammation and fibrosis.

Reactive oxygen species stimulate nuclear factor-kappa B (NF- κ B) and compounds that restore the “redox balance” of the cell ultimately inhibit NF- κ B (29). The components of the NF- κ B family of transcription factors are designated p50, p52, p65 (Rel A), c-Rel and Rel B; each derives from a separate gene product (30). This family forms dimeric protein complexes, is constitutively present in the cytoplasm of cells, and upon activation, translocates to the nucleus, where it, in turn controls genes contributing to tissue inflammation, cellular proliferation and cellular differentiation (30). NF- κ B can be activated by a number of stimuli including angiotensin II (31) and tumor necrosis factor alpha (TNF- α). Transcription factors of the NF- κ B family can directly or indirectly influence cellular events leading to tissue fibrosis.

Tumor Necrosis Factor- α

There are two members of the tumor necrosis factor (TNF) family: TNF- α and TNF- β . The discussion in this article will be confined to TNF- α . Activation of the human TNF- α gene leads to the production of a protein with 233 amino acids. The

Table 3. Factors whose Expression is Increased in the Kidney with Ureteral Obstruction

Transforming growth factor β (TGF- β_1)
Protein 53 (p53)
Protein 21 [p21, (WAF1)]
Tissue inhibitors of metalloproteinases-1 (TIMP-1)
Decorin
Nuclear factor- κ B (NF- κ B)
Tumor necrosis factor- α (TNF- α)
Vasoactive compounds
Angiotensinogen
Angiotensin II
Endothelin
Thromboxane A ₂
Prostaglandins
Proto-oncogenes
c-fos, c-jun, jun B, c-myc, cH-Ras
Growth factors
Interleukin-6 (IL-6)
Platelet activating factor (PAF)
Basic fibroblast growth factor (BFG)
Proteins involved in apoptosis
Clusterin (SGP-2)
Osteopontin
Chemoattractants
Monocyte chemoattractant peptide-1 (MCP-1)
Osteopontin
Adhesion Proteins
Intercellular adhesion molecule 1 (ICAM-1)
Vascular cell adhesion molecule 1 (VCAM-1)
Fibronectin alternate splice forms
Matrix/basement membrane proteins
Collagen types I, III and IV

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signal sequence of full length TNF- α is unusually long (76 amino acids). This signal sequence provides a mechanism by which TNF- α can exist as an integral membrane protein, with the carboxy-terminus extracellular. Mature TNF- α consists of 157 amino acids with a molecular mass of 17 kDa. Fully mature TNF- α protein self-assemble as homotrimers with masses of 51 kDa. The macrophage is a major source of TNF- α , but TNF- α is also produced by resident renal cells (32, 33). Two TNF- α receptors have been described: one with a molecular weight of 55 kDa (TNFR1) and the other with a molecular weight of 75 kDa (TNFR2) (34). Binding of TNF- α to its receptors activates a number of signal transduction pathways that result in the expression of a variety of transcription factors, cytokines, growth factors, receptors, cell adhesion molecules, mediators of inflammatory processes, acute phase proteins, and major histocompatibility complex proteins (34). Lipopolysaccharide (LPS)-induced renal injury is associated with increased expression of TNF- α by renal cells. Proximal tubular cells express TNF- α when stimulated with interleukin-1 α or LPS (35). Also, mRNA transcripts of TNF- α are found in cortical tubules of mice injected with LPS. Thus, resident renal cells (glomerular mesangial cells and tubular epithelial cells) are sources of TNF- α production in renal injury. We found (36) that in normal rats TNF- α mRNA was more abundant in glomerulitis than in renal cortical tubules. We measured TNF- α mRNA in the renal cortex of rats at different times after the onset of unilateral ureteral obstruction and determined whether angiotensin II inhibition or total body irradiation affected the mRNA levels of TNF- α (36). Cortical tubules obtained from the kidney with ureteral obstruction had a marked increase in TNF- α mRNA expression, whereas the glomeruli obtained from the same kidneys did not. Thus, upregulation of TNF- α expression was confined to renal tubular cells of the obstructed kidney. Levels of TNF- α mRNA are significantly increased in the obstructed kidney at 1 hour ($\times 2$), 2 hours ($\times 2.7$), 4 hours ($\times 3.6$), 24 hours ($\times 2.7$), 72 hours ($\times 1.8$) and 120 hours ($\times 2.8$) after ureteral ligation when compared to the contralateral kidney of the same rats or to the control kidney of normal rats. Administration of enalapril, an ACE inhibitor, before and during unilateral ureteral obstruction decreased TNF- α mRNA levels in the obstructed kidney by about 40% at 4 hours after the onset of obstruction. Total body irradiation, which prevents the migration of macrophages to the obstructed kidney, did not affect the upregulation of TNF- α mRNA expression at 4 hours after unilateral ureteral obstruction. Thus, TNF- α may have a role in initiating tubulointerstitial injury in the obstructed kidney. Leukocytes, infiltrating the renal interstitium of the obstructed kidney, do not appear to contribute to the increased expression of TNF- α mRNA. Angiotensin II seems to contribute, at least in part, to the early increase in expression of TNF- α mRNA in the obstructed kidney.

TNF- α has a role in the recruitment of inflammatory cells in animal models of glomerular injury. It stimulates the production of chemotactic factors by resident cells and upregulates monocyte chemoattractant protein-1 (MCP-1) mRNA in human mesangial cells. Wolf et al (37) found that TNF- α increases

RANTES mRNA in a murine mesangial cell line and *in vivo* in rat kidneys perfused with TNF- α . Mulligan et al (38) reported that anti-TNF- α or soluble recombinant human TNFR1 blocked the upregulation of intercellular adhesion molecule 1 (ICAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), and vascular adhesion molecule 1 (VCAM-1) in nephrotoxic nephritis. The above data support the concept that TNF- α contributes to the increased macrophage migration into the renal interstitium of the affected kidney. We found that macrophages infiltrated the interstitium of the obstructed kidney cortex as early as 4 hours after the onset of unilateral ureteral obstruction, and by 24 hours the influx was at a level approximately 10-fold greater than normal (39). Taken together, these observations suggest that an early increase in TNF- α after ureteral obstruction of the kidney upregulates the production of a chemoattractant(s) for monocytes and contributes to the infiltration of the obstructed kidney by leukocytes.

The binding of TNF- α to a cell surface receptor results in intracellular metabolic changes that mediate apoptotic and necrotic cell death (40, 41). Although the mechanism of the cytosolic action of TNF- α has not been completely elucidated, the TNFR1 receptor has been shown to have a cytoplasmic domain sequence similar to the Fas antigen receptor, which is considered to mediate apoptosis (42). Some investigators have reported apoptosis of renal tubular cells in the obstructed kidney one week after ureteral ligation (43, 44).

Effect of Pharmacologic Interventions in Obstructive Nephropathy

Administration of an ACE inhibitor or an angiotensin II receptor (AT1) antagonist, to rats with unilateral ureteral obstruction, ameliorated the increase in interstitial volume and attenuated the increased expression of TGF- β_1 in tubular cells, the increased production of extracellular matrix protein, the activation of NF- κ B, the proliferation of fibroblasts and the conversion of their phenotype to myofibroblasts (45). A monocyte/macrophage infiltrate was present in the obstructed kidney of untreated rats and in the obstructed kidney of rats treated with the angiotensin II receptor antagonist. By contrast, this infiltrate was markedly decreased in the obstructed kidney of rats treated with an ACE inhibitor. This difference may be owing to greater generation of nitric oxide related to increased levels of bradykinin during ACE inhibition (46). In fact, rats with unilateral obstruction given both an ACE inhibitor and (L-NAME) (an inhibitor of NO formation) had a substantial macrophage infiltrate. Administration of L-arginine in the drinking water significantly blunted the increases in interstitial volume, monocyte infiltration, interstitial collagen IV and α -smooth muscle actin expression (47). However, in contrast to ACE inhibitors, arginine administration did not decrease the expression of TGF- β_1 mRNA in the kidney with ureteral ligation. We also found a 10-fold increase in TIMP-1 mRNA in the obstructed kidney. Administration of an ACE inhibitor blunted this increase, by 40 % ($p < 0.001$). The addition of L-NAME to the ACE inhibitor prevented the decrease in TIMP-1 mRNA.

A common denominator of the beneficial effects of ACE inhibition or arginine and the deleterious effects of L-NAME during ACE inhibition may be a result of the increased or decreased generation of NO (46, 47).

In the above studies the ACE inhibitor was administered before or concomitant with the onset of ureteral obstruction. We also have examined the effects of ACE inhibition after 3 or 5 days of established unilateral ureteral obstruction in rats. Delayed administration of an ACE inhibitor slowed and in several instances halted the progression of fibrosis in the tubulointerstitium of the kidney with ureteral ligation (48).

Pharmacological maneuvers that reduce angiotensin II (ACE inhibitors) or interfere with its action (AT1 receptor antagonists) blunt NF- κ B activation and blunt the progression of disease. Although AT2 receptor inhibition decreases NF- κ B activation the effect on NF- κ B dimers may be different from those affected through AT1 receptors (45). Indeed, AT2 receptor inhibition in rats (49) or AT2 receptor knockout in mice (50) exacerbates renal fibrosis consequent to ureteral obstruction. Pharmacological maneuvers that reduce the activation of certain NF- κ B isotypes may extrinsically blunt angiotensin II-mediated effects and also slow the progression of renal disease.

In summary, angiotensin II regulates a number of genes associated with the progression of renal disease. The regulation of gene expression by angiotensin II occurs through specific receptors that are ultimately linked to changes in the activity of transcription factors within the nucleus of target cells. In particular, members of the NF- κ B family of transcription factors are activated, which, in turn, fuels at least two autocrine reinforcing loops that amplify angiotensin II and TNF- α formation. This amplification of the angiotensin II and TNF- α signals to the same cells in an autocrine manner or to adjacent cells in a paracrine manner further amplifies NF- κ B activation within the kidney. This leads to fibroblast proliferation and subsequent differentiation into myofibroblasts. Furthermore, tubular epithelial cells are stimulated to produce chemoattractants and adhesion proteins which cause an inflammatory response, leading to monocyte/macrophage infiltration. The tubule cells also produce profibrotic cytokines, leading to an overproduction of extracellular matrix proteins by all cell types. The net result is fibrosis of the tubulointerstitium and progression of renal disease.

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