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RENAL STRUCTURAL AND PHYSIOLOGICAL ALTERATIONS SUBSEQUENT TO UNILATERAL URETERAL OBSTRUCTION

By

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التأثيرات الضارة المصاحبة لتعاطي مياه البحـــر على تركيب وظيفـــة الكليـــة

زينـــب محمود أحمد الجوهري

اهتمت هذه الدراسة بتوضيح الآثار الضارة الحادثة بالكلية والمصاحبة لعملية ابتلاع مياه البحر كما يحدث في حالة ما يقرب الغرق . وقد تم تعاطي ٣ مم من مياه البحر لذكور الفئران البالغة يومياً ولمدة خمسة أيام متتالية وقد بينت النتائج التي توصل إليها هذا البحث ما يلي : انخفاض واضح في المحتوى الأيوني للكالسيوم والماغنيوم في بلازما الدم مع ارتفاع ملحوظ في محتواها الأيوني للصوديوم والبوتاسيوم وكذا زيادة تركيز اليوريا والكرياتنين . كما أوضحت الدراسة نقص ملموس في حجم البول المتكون مع زيادة معدل اخراج الصوديوم والكالسيوم والماغنسيوم بينما حدث نقص في معدل اخراج اليوريا والكرياتنين والبوتاسيوم بالاضافة إلى ذلك فقد حدث في نشاط انزيم Renal angiotensim — I — Converting enzyme في كل الحيوانات المعاملة مع حدوث بعض التهتكات الهستيولوجية بالكلية .

Key Words: Renal kidney structure, function, Ureteral obstruction.

ABSTRACT

Complete obstruction of the right ureter of male rabbits for eight weeks resulted in filling of the obstructed kidney with clear urine, no precipitation or stone formation. The calyces and pelvis were distinctly dilated with parenchymal atrophy, the medulla was almost completely destroyed and the cortex was reduced to a thin extensively sclerotic rim. When compared with the contralateral control kidney, the parenchymal weight and water content of the obstructed kidney were distinctly greater. From the histological point of view, some of the renal tubules were dilated, others atrophied and showed chronic interstitial inflammatory changes more sever than those in the glomeruli. Urinary sodium concentration of the obstructed kidney was significantly greater ($P< 0.01$) while that of potassium and urea were lower ($P < 0.01$) than those of the controls. In the obstructed kidney, the tissue concentration gradients of sodium, potassium and urea between the cortex and papillary tip were significantly lower ($P < 0.01$) in comparison to the control kindney. Also, renal Na-K-ATPase activity in the different zones of the obstructed kidney was greatly lower ($P < 0.01$) than those in control for all renal zones. While renal angiotensin-1-converting enzyme activity was higher in the obstructed kidney than that in control.

INTRODUCTION

Obstruction of the urinary tract occurs often and is a relatively common cause of renal failure (Klahr, 1983). Because obstruction generally is a remediable cause of kidney failure, early and accurate diagnosis and prompt implementation of appropriate therapeutic maneuvers assume considerable importance in the preservation and avoiding irreversible loss of renal function (Paltiel and Lebowitz, 1989), that occurs with prolonged and complete obstruction. Urinary tract obstruction has been widely utilized as a tool for studying certain aspects of renal function. Diminished renin production and/or storage capacity, hyperkalemia and damage to the renal medulla and distal tubules are demonstrated in hydronephrotic rat kidneys (Susic *et al.*, 1975).

Urinary tract obstruction leads to many alternations in renal hemodynamics and tubular function including progressive azotemia due to decreased glomerular filtration rate (GFR) (Bander *et al.*, 1985), a defect in urinary concentrating ability (Susic *et al.*, 1975). Also, obstruction leads to changes in sodium, potassium excretion and urinary acidification (Berlyne, 1961; McDougal and Persky, 1975; Susic *et al.*, 1975; Klahr, 1983).

Furthermore, increase in the intraluminal pressure of the ureter and renal tubules is one of the earliest detectable effects of urinary tract obstruction (Dalcanton *et al.*, 1980; and Wright, 1982).

The present study was designed to reveal the structural and physiological renal response of adult male rabbits to complete unilateral proximal obstruction of the right ureter.

MATERIALS AND METHODS

1. Animals and experimental design

Fifteen adult male rabbits 6-9 month old, each weighting 1-1.5Kg. were used. Under light ether anesthesia, the right ureter of each animal was exposed through an abdominal incision and completely obstructed below the ureteropelvic junction without interference with the renal vessels. Then the abdomen was closed and the operated animals were allowed free access to water and food for eight weeks, after which they were sacrificed. Kidney size was determined by water replacement method. Urine samples were collected from the renal pelvis of both obstructed and control kidneys of each animal to measure sodium, potassium and urea concentrations. Both kidneys of each animal were removed rapidly and weighed separately. Kidneys of eight rabbits were divided into two halves, one half was used for histological studies, while the other half for measuring the renal concentration gradient of sodium, potassium and urea in cortical, medullary and papillary renal tissues. Kidneys of the other seven rabbits were used for measuring water content, renal angiotensin converting enzyme activity and Na-K-ATPase activity in cortical, medullary and papillary regions.

2. Analytical procedures

a. Water content

Known weight of fresh renal tissue from obstructed and control kidneys were dried to constant weight at 90°C for 48h. The percentage of water content was calculated from the difference between the weight of fresh and dried renal tissue.

b. Sodium and potassium concentrations in renal tissue and urine

Equal weights (0.5g) of renal tissues from different zones; cortex, medulla and papilla were dried at 90°C to constant weight. The dried tissue was then digested completely by concentrated nitric acid. The digested renal homogenate was diluted to a definite volume by bidistilled water for measuring renal sodium and potassium concentrations using an atomic absorption spectrophotometer.

c. Renal urea concentrations

Urea concentration in urine as well as in the different zones of renal tissue was determined colorimetrically by the method of (Foster and Hochhlozer, 1971).

d. Renal Na-K-ATPase and angiotensin-1-converting enzyme activities

Crude kidney homogenate preparation, Na-K-ATPase in the cortical and medullary zones angiotensin-1-converting enzyme activity assays performed as previously described (El Gohary, 1986 and 1990).

3. Histological preparation

Histological sections 6μm thick were prepared from formalsaline fixed, paraffin-wax embedded material and stained with haematoxylin and eosin.

4. Statistical analysis

The means and standard errors were calculated for each criterian and the data were compared using paired Student "t" test. Values of $P < 0.05$ were considered to indicate significant difference between the means.

RESULTS

1. Macroscopic observations

No mortality occurred after surgery. The obstructed kidney size (9.01 cm) was 223.5% greater than the control size (4.03 cm). The obstructed kidney was rounded with flattened renal papilla. The renal capsule was markedly stretched and tightly adhering to the kidney. The renal parenchyma was markedly fragile, yellowish grey in colour. Fibrous tissue proliferation was obvious in the vicinity of the obstructed kidney. The great hydronephrosis was easily detected in the obstructed kidney. It was so dilated that its wall was transparent while the renal papilla was narrow and cystic spaces occurred in the renal parenchyma, typically at the cortico-medullary junction.

2. Kidney weight and water content

Obstructed kidney (9.5g+/−0.02) was significantly heavier and its water content (78%+/−1.3) was significantly higher than the corresponding values in the contralateral unobstructed kidney (4.8g+/−0.3, 62%+/−0.8) respectively, as shown in Table 1.

Table 1

Kidney weight (g) and water content (%) of obstructed and control kidney.

	Kidney weight (g)	Water content (%)
Obstructed kidney	9.5+/−0.2	78+/−1.3
Control kidney	4.8+/−0.3	62+/−0.8

3. Histological observations

Necrotic changes occurred in the entire tissues of the obstructed kidney. The tubules were often filled with eosinophilic cellular debris (Fig. 1). The stroma was infiltrated with rounded cells mixed with numerous polymorphonuclear cells and macrophages accompanied with tissue disintegration with loss of structure (Fig. 2). The renal cortex of the obstructed kidney was largely composed of glomeruli separated by only connective tissue fib rils and minute unidentifiable tubular remnants (Fig. 3). Compression of the capillary tuft resulted in Bowman's space enlargement; the latter frequently contained some coagulated fluid. Bowman's membrane was slightly thick than that of the control (Fig. 4). In obstructed kidney, variability in the size and shape of glomeruli was greater when compared with those of the control (Fig. 5). The lumen diameter in the majority of the renal tubules was greater and the epithelial linning was of variable thickness. However, some tubules were compressed (Fig. 6). In some tubules, the cells exhibit marked degeneration or vaculation of their cytoplasm. Loops of Henle were compressed owing to dilatation of the collecting tubules between which they lie (Fig. 7). The distal convoluted tubules displayed dilatation with marked epithelial atrophy. Red blood corpuscles were observed in both the distal convoluted and collecting tubules (Fig. 6). A dense zone of hyaline collagen occurred at the corticomedullary boundary. Generally, the obstructed kidney was not only grossly hydronephrotic but also dysplastic by histologic criteria; including parenchymal disorganization, marked fibrosis, while the contralateral unobstructed kidney was normal (Fig. 8-10).

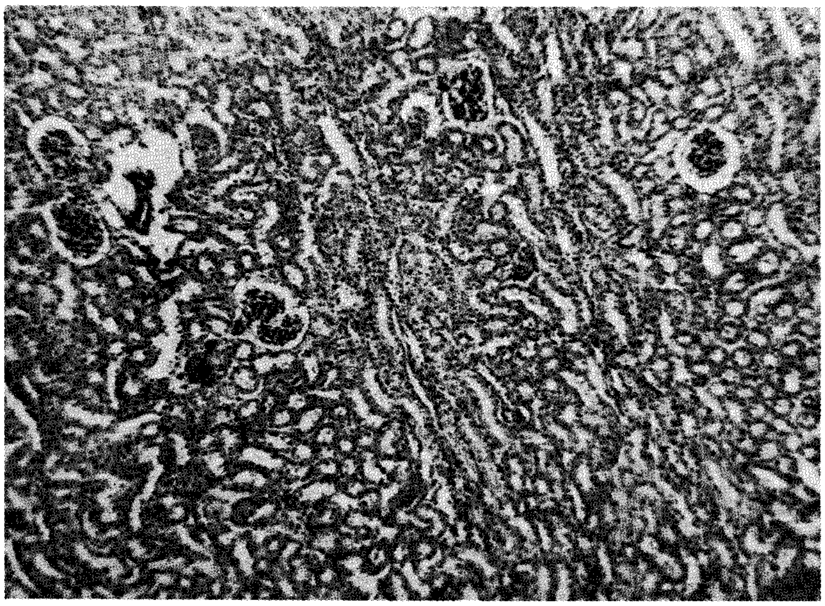

Fig. 1: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows necrotic renal tubules. EH × 100

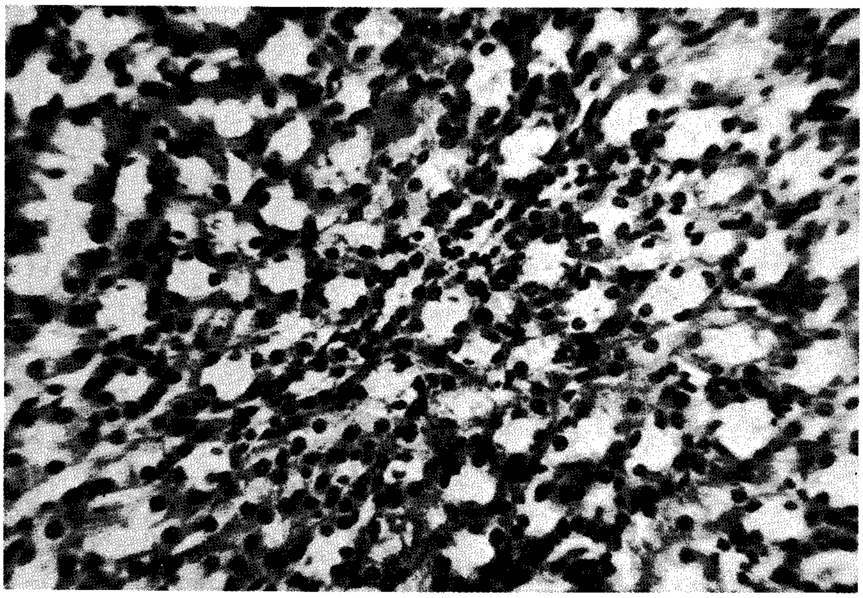

Fig. 2: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows renal tissue disintegration with loss of structure. EH × 100

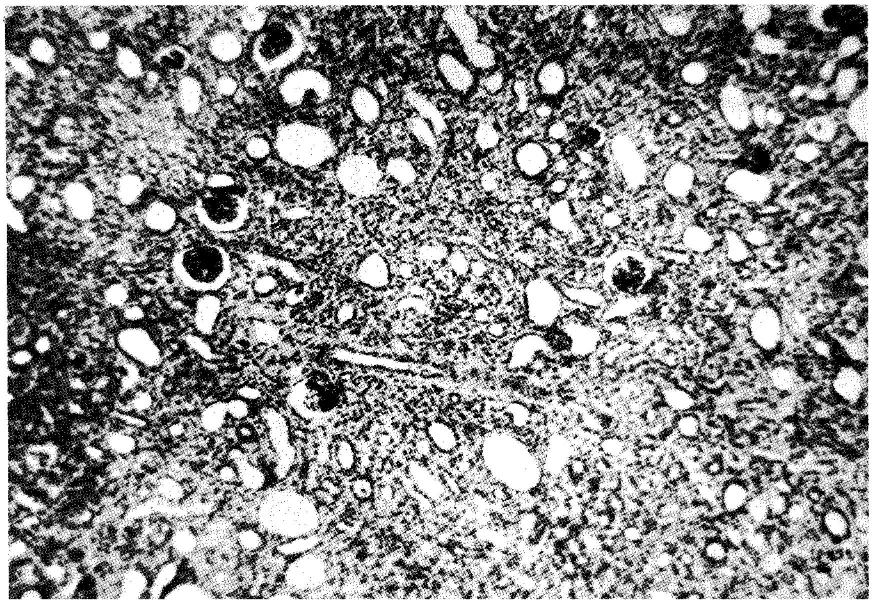

Fig. 3: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows the renal cortex of the obstructed kidney which was largely composed of glomeruli separated by only connective tissue fibrils and minute unidentifiable tubular remnants. EH × 100

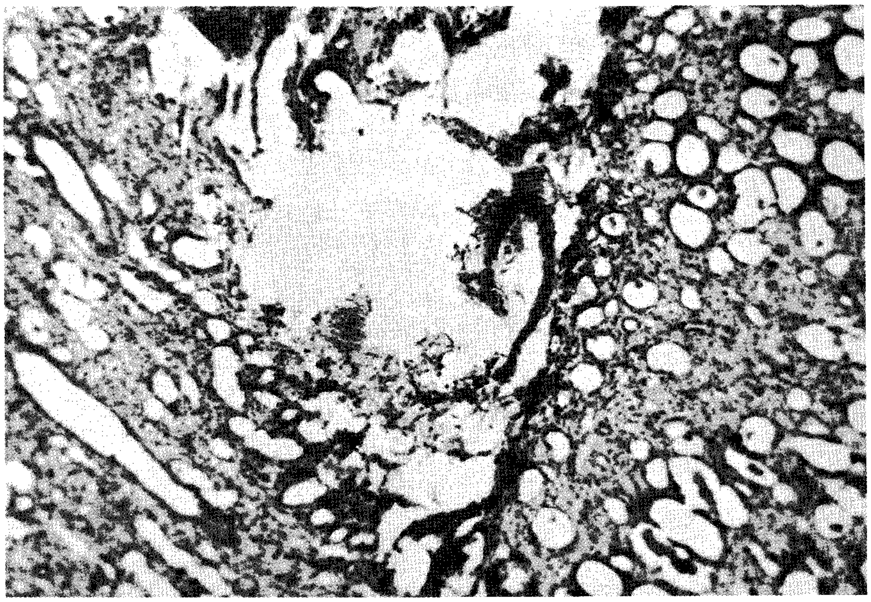

Fig. 4: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows enlargement of Bowman's space due to compression of its capillary tuft. EH × 100

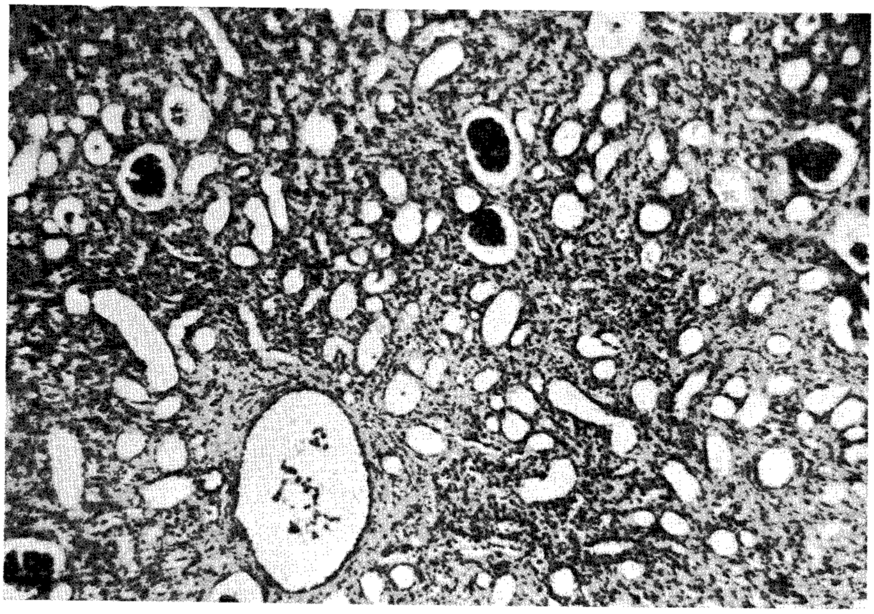

Fig. 5: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows great variability in the size and shape of glomeruli. EH × 100

Fig. 6: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows relative great diameter of the majority of renal tubules. EH × 100

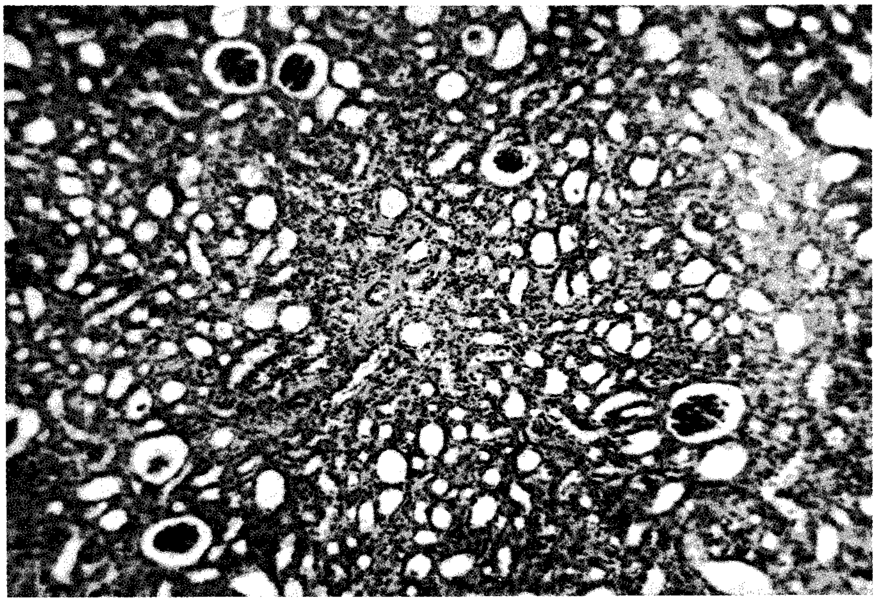

Fig. 7: A photomicrograph of a transverse section in the obstructed kidney of male rabbit shows dilatation of the collecting ducts and compression of the loops of Henle with marked epithelial necrosis. EH × 100

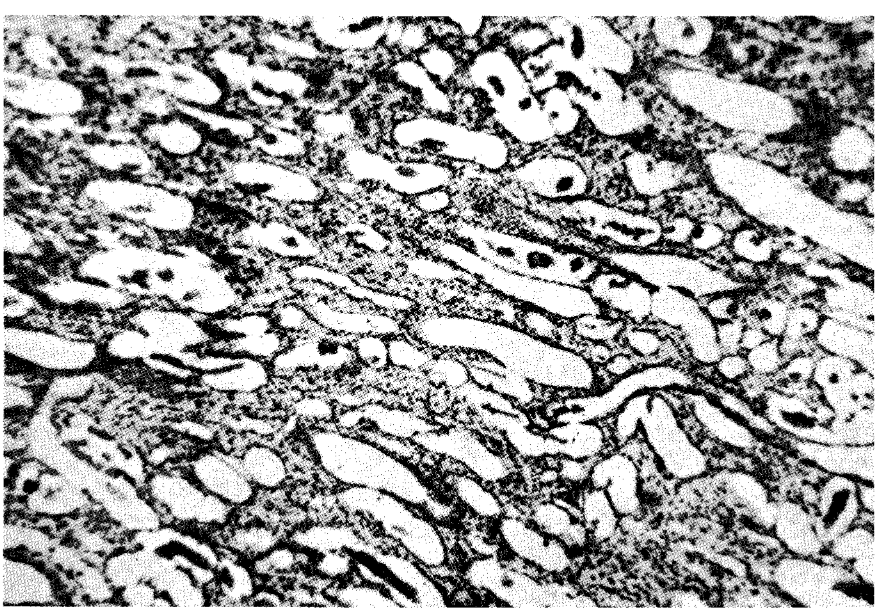

Fig. 8: A photomicrograph of a transverse section in the control kidney of male rabbit shows normal structure of renal cortex. EH × 100

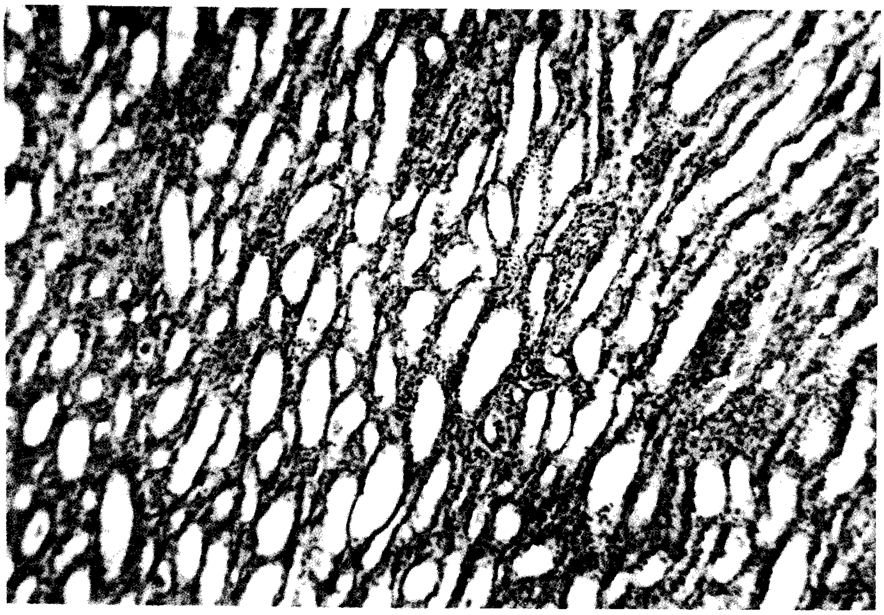

Fig. 9: A photomicrograph of a transverse section in the control kidney of male rabbit shows normal appearance of glomeruli, proximal and distal convoluted tubules. EH × 400

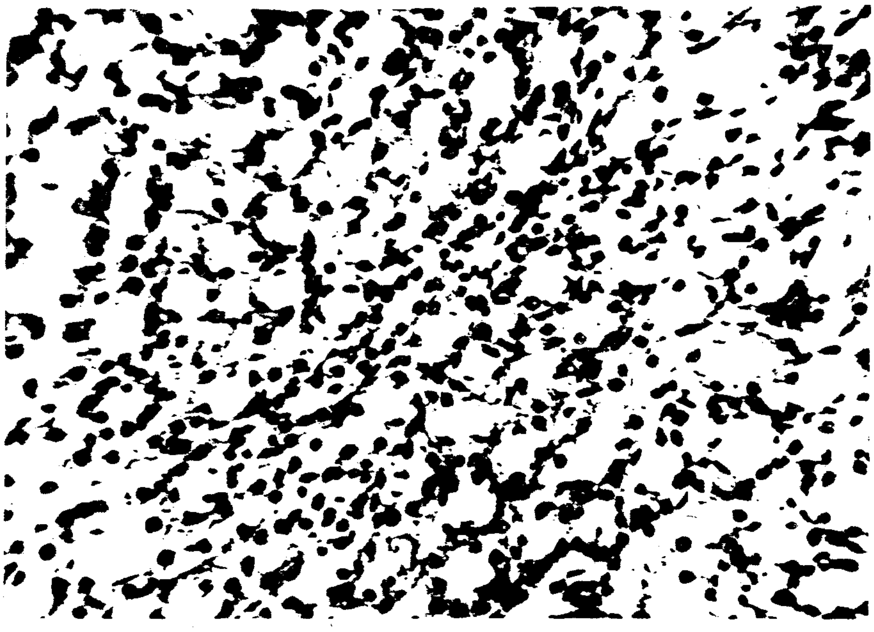

Fig. 10: A photomicrograph of a transverse section in the control kidney of male rabbit shows normal structure of renal medulla. EH × 100

4. Electrolyte concentrations

a. Urine

Urine sodium concentration from the obstructed kidney (120+/−2.3 mmol/L) was significantly higher ($P < 0.001$) than that from control kidney (90+/−1.4 mmol/L) (Table 2). On the other hand, both urine potassium (92+/−2.4 mmol/L) and urea (84.5+/−4.8 mM) concentrations from the obstructed kidney were significantly ($P < 0.001$) lower than the corresponding values (160+/−3.1 mmol/L and 110+/−1.1 mM respectively) in urine from control kidney (Table 2).

Table 2
Sodium (Na), potassium (K) and urea concentrations in urine from obstructed kidney (Obst. K.) and control kidney (Con. K.) as well as in different renal zones (Renal Z.); cortex (Cort.), medulla (Med.) and papilla (Pap.) of obstructed and control kidney. All data are expressed as means +/−SE.

Exp. parameter	Na. (mmol/L)	K. (mmol/L)	Urea (mM)
Urine Obst. K.	120+/−2.3	92+/−2.4	84.5+/−4.8
Con. K.	90+/−1.4	160+/−3.1	110+/−1.1
Renal Z. Obst. K.			
Cort.	35+/−1.3	60.4+/−2.6	18.3+/−1.1
Med.	72+/−2.6	75.9+/−2.8	120+/−2.1
Pap.	65.4+/−0.5	88.7+/−1.6	140+/−1.5
Con. K.			
Cort.	52.7+/−1.4	95.7+/−2.4	29.4+/−1.3
Med.	98.9+/−2.1	87+/−3.1	103.9+/−2.1
Pap.	185.4+/−2.3	76.9+/−2.5	333.6+/−1.6

b. Renal tissue

In the cortical, medullary and papillary zones, concentration of sodium (35+/−1.3, 72+/−2.6 and 65.4+/−0.5 mmol/g respectively), potassium (60.4+/−2.6, 75.9+/−2.8, 88.7+/−1.6 mmol/g respectively) and urea (18.3+/−1.1, 120.4+/−2.1 and 140+/−1.5 mM respectively) were consistently lower ($P < 0.01$) for the obstructed kidney than the corresponding values for the control kidney (Sodium, 52.7+/−1.4, 98.9+/−2.1, 185.4+/−2.3 mmol/g respectively; potassium, 95.7+/−2.4, 87+/−3.1, 76.9+/−2.5 mmol/g respectively; urea, 29.4+/−1.3, 103.9+/−2.1, 333.6+/−1.6 mM respectively) (Table 2).

5. Renal Na-K-ATPase and angiotensine-converting enzyme activities

Renal Na-K-ATPase activity in crude renal homogenate from the cortex and the entire medulla were 3.5+/−0.1 μmole Pi/mg protein/h and 6.3+/−1.2 μmole Pi/mg protein/h respectively for obstructed kidney. These values were significantly lower ($P < 0.001$) than the corresponding values (6.8+/−0.1 μmole Pi/mg protein/h and 22.5+/−0.3 μmole Pi/mg protein/h respectively) for control kidney. In contrast, renal angiotensin-1-converting enzyme (AC) activity (12.3+/−0.3 μmole hippuric acid/mg protein/h) in the obstructed kidney homogenate was significantly higher ($P < 0.01$) than that in the control one (5.1+/−0.2 μmole hippuric acid/mg protein/h, (Table 3).

Table 3
Renal Na-K-ATPase (μmole Pi/mg protein/h.) and angiotensin-1-converting enzyme (AC) (μmole hippuric acid/mg protein/min) activities in obstructed and control kidnev.

	Na-K-ATPase		(AC)
	Cort.	Med.	
Obstructed kidney	3.5+/−0.1	6.3+/−1.2	12.3+/−0.3
Control kidney	6.8+/−0.1	22.5+/−0.3	5.1+/−0.2

DISCUSSION

In the present study, obstruction of one ureter provided adequate functional renal mass in the contralateral kidney for survival of the rabbit. This technique also minimized the compensatory hypertrophy occurring in response to the initial reduction in total renal mass. Also, the unobstructed contralateral kidney provided an excellent intra-individual control in the present model.

In the present study, obvious alterations subsequent to this obstruction included marked increase in the obstructed kidney weight probably owing to congestion, edema and accumulation of fluid in the dilated tubules as demonstrated in the high water content.

Also, histological investigations revealed that the interstitial tissue of the obstructed kidney was edematous and exhibited cellular infiltration and fibrosis within the parenchyma of both cortex and atrophied medulla. These histological changes are similar to those described by (Cylwik *et al.*, 1985) in the dog and (Fortyne *et al.*, 1987) in the rat and pig. Elevated pressure in the renal pelvis and calyces consequent to obstruction (Wright, 1982), may be directly responsible for the demonstrated medullary atrophied.

The higher sodium concentration urine from the obstructed rat kidney in the present study is in-agreement with the results of (Klahr, 1983), and such elevation may be attributed to impairment of deep nephron function and distal nephron reabsorption (Wilson, 1972, 1974 and Wilson and Honrath, 1975), as a consequence to destruction of the medullary region. Enhanced prostaglandin (PG) biosynthesis in hydronephrotic kidney (Nishikawa *et al.*, 1977), may explain the reduction in sodium reabsorption and naturesis associated with ureter obstruction since prostaglandins are known to be naturetic (Johnson *et al.*, 1967). Elevated sodium in the obstructed kidney urine is paralled with low renal Na-K-ATPase activity, since Na-K-ATPase is involved in sodium reabsorption (Katz and Epstein, 1968).

The lower urinary potassium concentration of the urine from the obstructed kidney may be related to reduction in sodium delivery and in tubular flow rate in the distal nephron (McDougal and Wright, 1972).

The low urea concentration in urine from the obstructed kidney reflects its poor concentrating ability. Also increased urea reabsorption in the distal nephron may explain the fall in urea concentration in the urine from obstructed kidney.

In the present study, tissue concentration gradient of sodium, potassium and urea between the cortex and papillary tip was abolished in the obstructed kidney. The results are in agreement with the findings of (Berlyne and Macken, 1962; Eknoyan *et al.*, 1970; and Suki *et al.*, 1971) in dogs and Honda *et al.*, (1971) in rabbits. Further support comes from the study of (Hanley and Davidson, 1982), who reported a marked decrease in chloride transport in the thick ascending limb of Henle's loops microdissected from obstructed rat kidneys and perfused in vitro.

Lowered renal Na, K and urea concentrations in the different renal zones of the obstructed kidney is related either to decrease in the amount of sodium and potassium transported into the interstitium as a result of the non-filtering nephrons, a consequence to the elevated ureteral pressure (Malvin *et al.*, 1964; DalCanton *et al.*, 1980 and Wright, 1982), or to washout of solute from interstitium due to elevated medullary blood flow (Wilson, 1980 and Klahr, 1983). Also, a defect in the transtubular transport of NaCl in the ascending limb of the loop of Henle in the obstructed kidney (McDougal and Persky, 1975) would lower the tonicity of the medullary interstitium and, thus, the osmotic driving force for water movement from the collecting duct into the interstitium (Schmidt-Nielsen and O'Dell, 1961).

The results of this study demonstrate a striking inhibition of renal Na-K-ATPase activity in both cortex and medulla of the obstructed kidney, which was more marked in the medullary zone. Such reduction is consistent with the demonstrated severe necrotic tubular epithelium, where the enzyme localized. The detected decrease in renal Na-K-ATPase activity of obstructed kidney are comparable with the results of Williams *et al.* (1976), on dogs and Wilson *et al.* (1974, 1978) on rats. In agreement with the present results, Eknoyan *et al.* (1970) and Buerkert *et al.* (1977) reported impairment in the maximal concentrating ability and capacity to reabsorb solute -free water in obstructed rat kidney whereas Na-K-ATPase plays an important role in the bulk reabsorption of sodium by the kidney (Katz and Epstein, 1968).

The demonstrated elevation in the angiotensin-1-converting enzyme activity in the obstructed rat kidney in the present study is comparable with the results of Kaloyanides *et al.*, (1973), who reported increased renal renin release with ureteral obstruction in rats and with the findings of Wideman and Gregg, (1988), who reported reduction in glomerular filtration rate (GFR), consequence to ureteral obstruction in the chick. Also, the present results are consistent with the studies of Nishikawa *et al.*, (1977), who demonstrated increased prostaglandin synthesis in the hydronephrotic isolated perfused kidney and with the findings of Yarger and Harris, (1978) and Yarger *et al.*, (1980), who noted improvement of GFR and renal blood flow in the obstructed rat kidney after administration of an angiotensin-1-converting enzyme inhibitor, captopril.

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