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Urinary excretion of tubular proteins and the technetium-99m dimercaptosuccinic acid (DMSA) absolute renal uptake in partial ureteral obstruction in rats: a functional evaluation of hydronephrotic kidneys

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Abstract The aim of this longitudinal study was to evaluate tubular proteinuria in rats with unilateral (UPO) and bilateral (BPO) partial ureteral obstruction with the dimercaptosuccinic acid (DMSA) scan as the gold standard for measuring renal tubular damage. We studied 70 female Wistar rats: 28 animals with UPO, 28 animals with BPO, 7 sham-operated animals, and 7 controls. All animals with obstructed ureters showed renal dilatation on the diethylenetriaminepentaacetic acid DTPA images 1 and 5 weeks postoperatively. One week following UPO and BPO, tubular proteinuria and urinary *N*-acetyl-beta-D-glucosaminidase (NAG) activity increased ($P < 0.01$) and the absolute DMSA uptake decreased ($P < 0.01$). Persistently (week 6) high tubular proteinuria was found in 29% of the animals and was related to severe damage on the DMSA scan ($P < 0.01$) and to albuminuria ($P < 0.05$). Renal tubular damage was demonstrated by measuring renal enzymes, tubular proteins, and DMSA uptake after UPO and BPO. Persistent elevated tubular proteinuria was related to severely damaged kidneys.

Key words Ureteral obstruction · Proteinuria · Tubular proteins · Hydronephrosis · DMSA

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Introduction

A ureteral obstruction rapidly provokes renal tubular damage [1, 3, 4, 6, 10–12], and the appearance of tubular proteins or renal enzymes in urine has proven to be a valuable indicator of damage to the proximal tubule [3, 4, 6]. Tubular proteins have a low molecular mass (< 68 kDa) and so are filtered through the glomeruli and reabsorbed very efficiently by the proximal tubules. Only extremely low concentrations of tubular proteins appear in urine in physiological situations. Damage to the reabsorption mechanism results in leakage of these small proteins into the urine. The literature reports this occurring after obstruction, intoxication with heavy metals, diabetes, and pyelonephritis. Several such tubular proteins are described: beta-2-microglobulin, retinol-binding protein, and alpha-1-microglobulin [3, 7, 10, 15, 20–21]. Renal enzymes like gamma-glutamyl transferase (a brush-border enzyme), lysozyme, and *N*-acetyl-beta-D-glucosaminidase (NAG) (both lysozomal enzymes of the tubular cells) appear in urine after the tubular cell membranes have been damaged [6, 9]. Tubular proteinuria is more accesible for routine purposes, and its analysis is less prone to the influence of the variability of the urine composition compared with the renal enzymes . To our knowledge, no other

longitudinal studies on the evolution of tubular proteins after partial obstruction have yet been performed.

Huland et al. [6] evaluated semilongitudinally the NAG activity as a parameter of the destructive phase after unilateral partial ureteral obstruction in rats. In the unipapillar kidney (rat), the destructive phase lasts for 2 weeks and then stable atrophy is established [5, 12]. During the destructive phase, urinary NAG activity was elevated significantly [6]. However, in Huland's study, a contralateral nephrectomy was performed in all animals and the study was semilongitudinal, which are not common clinical situations.

Renal diethylenetriaminepentaacetic acid (DTPA) images reveal the morphology of the outflow tract (dilatation) but do not measure the extent of tubular damage caused by the obstruction. At present, ^{99m}Tc dimercaptosuccinic acid (DMSA) scintigraphy is considered the gold standard for the evaluation of renal tubular damage [1, 11, 19]. However, repeated evaluation is needed to quantify the residual functional tubular mass over time and to differentiate the destructive phase (ongoing tubular damage) from the steady-state phase [1, 19]. If we can confirm Huland's experiment in a more clinically realistic setting, the combined use of tubular proteinuria might help to stage each individual animal in the time course after partial ureteral obstruction.

The aims of the study were (1) to confirm Huland's experiments in a more clinically realistic setting (no contralateral nephrectomy, longitudinal instead of semilongitudinal), (2) to demonstrate tubular proteinuria in an animal model of unilateral and bilateral partial ureteral obstruction and use Tc-99 m DMSA scintigraphy for measuring renal tubular damage and ^{99m}Tc DTPA renography for the diagnosis of ureteropelvic dilatation and (3) to see if the combined use of the ^{99m}Tc DMSA scintigraphy and tubular proteinuria stages each animal in the time course after partial ureteral obstruction.

Subjects and methods

Animals

The experiments were performed on 70 female Wistar rats weighing 200 to 300 g. Unilateral partial ureteral obstruction (UPO) was performed on 28 animals (5 died, 23 survived). Bilateral partial ureteral obstruction (BPO) was performed on 28 animals (6 died, 22 survived), and a sham procedure on 7 animals; a further 7 animals were included as controls. Of these 70 animals, 11 died during the protocol (before week 7) and were excluded from the study. Animals dying during week 7 were not excluded.

Methods

Operations were performed under general anaesthesia using pentobarbital (Nembutal) intraperitoneally at 40 to 60 mg/kg body weight. At the end of week 1, a laparotomy was performed under microscope, and a unilateral or bilateral partial ureteral obstruction was created with the method described by Ulm and Miller [18]: the psoas was divided for a length of 2 cm, and the ureter was placed in the psoas muscle using two non-absorbable monofilament 8-O sutures (Ethicon). The UPO was always created on the right side.

In weeks 1, 2 and 6, three urine samples were collected in the morning [9, 20]. The samples of every individual were pooled per week. The animals were placed on a glass or transparent plastic plate and urine was obtained by spontaneous micturition. The urine was collected by aspiration and stored at −20°C. At week 7 (during laparotomy), urine was collected by bladder puncture for culture, and a blood sample was taken.

All samples were centrifuged at 5000 rpm for 5 min. The determination of the urinary NAG activity was used to diagnose tubular enzymuria. For the determination of the urinary NAG activity, we used a colorimetric assay (Boehringer Mannheim, Germany). The NAG activity (U/l) was measured photometrically at 580 nm. Serum and urine creatinine was assayed with Jaffé's method with commercial reagents (Boehringer Mannheim). Urinary NAG excretion was expressed per gram of urinary creatinine to rule out the influence of urinary dilution or concentration [9, 20–21].

Tubular proteinuria and albuminuria were measured by means of gel permeation chromatography using a protein Pak Glass 300 5 W (Waters) column on an advanced protein purification system (Waters 650, Millipore, Milford, Mass.). Photometric detection of proteins occurred at 280 nm. The elution buffer was phosphate-buffered saline (pH = 7.3; 0.1 M). The injection volume was 25 µl, and the run time was 40 min at a flow rate of 0.8 ml/min. Integration of the 10–15 kDa fractions was considered as the tubular protein fraction. Tubular proteinuria and albuminuria were expressed per gram of urinary creatinine to rule out the influence of urinary dilution or concentration [9, 20–21].

Long-lasting renal dilation following surgery was proved by means of a ^{99m}Tc DTPA renography and the extent of renal destruction (loss of tubular function) was determined with a ^{99m}Tc DMSA 24-h absolute uptake measurement. ^{99m}Tc DTPA and ^{99m}Tc DMSA scintigraphy was performed on the UPO, BPO and sham animals at weeks 2 and 6. Paired ^{99m}Tc DTPA and ^{99m}Tc DMSA scintigraphy results of weeks 2 and 6 were obtained as these are the most relevant ones for the purpose of the study. The results of ^{99m}Tc DMSA uptake at week 1 were obtained from the control population.

Both the ^{99m}Tc DTPA scintigraphy and ^{99m}Tc DMSA scintigraphy were performed with a single-headed camera equipped with a low-energy, all-purpose (LEAP) collimator (Toshiba GCA 40-Amp GGA-901A, Japan). The animals were anaesthetized with pentobarbital (Nembutal) intraperitoneally at 40 to 60 mg/kg and positioned on the back and in a 0.5 cm thick Plexiglas box placed on top of the collimator. For the ^{99m}Tc DTPA renography, 0.5 mCi of ^{99m}Tc DTPA was injected into an exposed jugular vein and then 200 × 6 s frames were taken. The acquisition was terminated at 20 min, and the images were analysed for the presence of outflow obstruction. Immediately after ^{99m}Tc DTPA renography, 0.5 mCi of ^{99m}Tc DMSA was injected, and the residues left in syringes were counted and timed. After 24 h, again under anaesthesia, ^{99m}Tc DMSA uptake was measured and regions of interest were drawn over each kidney and over a background area. The observer was blinded to the nature of the operation the animals had undergone. The renal uptake, expressed as a percentage of the total dose injected, was then calculated after deduction of the background activity. The grade of obstruction was assessed according to Provoost et al. [16] using an obstruction score. The obstruction score was derived from the time to reach the peak activity (graded from 0 to 3) and the renal activity at 15 min after ^{99m}Tc DTPA injection (graded from 0 to 3). The total obstruction score was the sum of both elements.

Statistical analysis

The data are given as medians and quartile range [median (range)]. The groups were compared by means of non-parametrical tests

(Mann-Witney U-test, Wilcoxon, Kruskal-Wallis). The correlations were calculated using a Spearman-rank correlation coefficient. A receiver operating curve (ROC) was used to determine sensitivity, aspecificity, and cut-off values.

Results

Assessment of functional ureteral obstruction with combined ^{99m}Tc DTPA and ^{99m}Tc DMSA scintigraphy

According to the ^{99m}Tc DTPA scintigraphy at weeks 2 and 6, all the kidneys were dilated on the right side following UPO and bilaterally following BPO. No dilatation was observed in the left kidney following UPO and in the kidneys of the sham group (weeks 2 and 6) or in the control group (week 1). Obstruction scores are depicted in Table 1. Non-obstructed kidneys and kidneys of sham and control animals had an obstruction score from 0 to 2.

Table 1 Grade of obstruction assessed with the technetium-99m (^{99m}Tc) diethylenetriaminepentaacetic acid (DTPA) renography

Obstruction score	No. of surgically obstructed kidneys at week 2	
	UPO (n = 23)	BPO (n = 44)
0	0	0
1	0	2
2	0	2
3	2	4
4	0	3
5	11	13
6	7	19
No ^{99m}Tc DTPA activity	3	1

UPO unilateral partial ureteral obstrunction, *BPO* bilateral partial ureteral obstruction. Obstruction score derived from the time to reach the peak activity (graded from 0 to 3) and renal activity at 15 min after ^{99m}Tc DTPA injection (graded from 0 to 3). The total obstruction score is the sum of both elements [16]. Non-obstructed kidneys and kidneys of sham and control animals had an obstruction score of 0 to 2

No significant differences in absolute ^{99m}Tc DMSA uptake were found between the kidneys of the control group at week 1 and the kidneys of the sham-operated rats at weeks 2 and 6 (Table 2). No significant differences in absolute ^{99m}Tc DMSA uptake were found between the left and the right kidneys of the control population at week 1 or the sham population at weeks 2 and 6 (Table 2).

Results of absolute ^{99m}Tc DMSA uptake in the UPO and BPO groups are given in Table 3 and Fig. 1. Following UPO, at week 2 (1 week after surgery), the ^{99m}Tc DMSA uptake was significantly ($P < 0.01$) less in the obstructed kidney (right) then in the unobstructed left kidney or the sham and control kidneys. There was significant ($P < 0.01$) improvement in ^{99m}Tc DMSA uptake of the obstructed (right) kidney from week 2 to week 6. The individual results of ^{99m}Tc DMSA uptake show ipsilateral recuperation in all animals. No significant difference was found in the left kidney from week 2 to week 6.

The results of the absolute ^{99m}Tc DMSA uptake following BPO are given in Table 3. At week 2 (1 week after surgery), the ^{99m}Tc DMSA uptake was significantly ($P < 0.05$) less in the obstructed kidneys than in the sham and control populations. The paired results of ^{99m}Tc DMSA uptake at weeks 2 and 6 of all the kidneys are shown in Fig. 1.

No significant difference was found between loss of absolute DMSA uptake in UPO (loss of right versus the left kidney: 12.7% (8.8%–18.5%)) and BPO (loss of both kidneys compared to the controls: 15.7% (1%–14.8%) group ($P > 0.10$).

Urinary NAG activity, tubular proteinuria, and albuminuria following UPO and BPO and the sham and control group

The urinary NAG activity, tubular proteinuria and albuminuria in the UPO and BPO groups at weeks 1, 2 and 6 are given in Table 3 and Fig. 2. Postoperatively (week 2) we found significant increases in the urinary

Table 2 Markers of tubular function in the sham population and the control group

	Week 1	Week 2	Week 6
Controls (n = 7)			
NAG, U/g creatinine	36.2 (16.1–43.0)	23.4 (22.1–61.9)	36.7 (26.0–57.1)
TP, mg/g creatinine	0 (0–0)	0 (0–0)	0 (0–0)
ALB, mg/g creatinine	0 (0–0)	0 (0–0)	43.9 (0–87.2)
DMSA, right kidney, %	25.9 (22.5–33.4)	–	–
DMSA, left kidney, %	25.2 (22.8–32.4)	–	–
Sham (n = 7)	Prior to surgery, week 1	Week 2	Week 6
NAG, U/g creatinine	17.6 (14.7–34.9)	22.2 (18.0–23.0)	27.8 (24.0–32.3)
TP, mg/g creatinine	0 (0–0)	0 (0–0)	0 (0–0)
ALB, mg/g creatinine	0 (0–86.1)	0 (0–0)	22.9 (0–51.2)
DMSA, right kidney, %	–	25.6 (22.0–28.5)	24.9 (21.0–27.0)
DMSA, left kidney, %	–	24.9 (21.5–26.5)	24.1 (21.0–25.5)

NAG *N*-acetyl-beta-D-glucosaminidase activity, *TP* tubular proteinuria, *ALS* albuminuria, *DMSA* absolute ^{99m}Tc dimercaptosuccinic acid
Data as median (lower-upper quartile)

Table 3 Markers of tubular function following partial ureteral obstruction

	Prior to surgery, week 1	Week 2	Week 6
UPO (n = 23)			
NAG, U/g creatinine	20.3 (16.0–28.8)	29.1 (20.3–38.7)°	25.6 (19.9–34.6)
TP, mg/g creatinine	0 (0–12.0)	50.3 (18.7–275.9)°°	0 (0–17.2)
ALB, mg/g creatinine	0 (0–94.1)	35.7 (0–317.4)	32.8 (0–282.4)
DMSA, right kidney, %	–	16.4 (12.4–19.2)**	22.8 (20.6–24.9)°°
DMSA, left kidney, %	–	22.5 (18.2–28.4)	24.6 (21.3–27.5)
BPO (n = 22)			
NAG, U/g creatinine	23.4 (16.5–34.9)	35.8 (27.6–50.8)°	30.7 (23.3–53.8)
TP, mg/g creatinine	0 (0–0)	84.0 (40.1–146.0)°°	26.4 (0–104.0)
ALB, mg/g creatinine	0 (0–190.6)	0 (0–35.0)	0 (0–143.4)
DMSA, both kidneys, %	–	20.9 (11.7–25.0)*	24.1 (19.3–28.0)

Data as median (lower-upper quartile)
* $P < 0.05$ versus controls and sham, all kidneys; ** $P < 0.01$ versus controls and sham, all kidneys; ° $P < 0.05$ versus previous test result; °° $P < 0.01$ versus previous test result

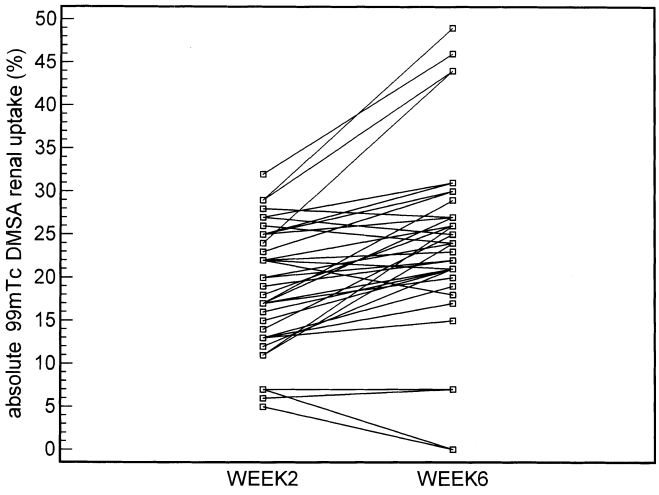

Fig. 1 Absolute dimercaptosuccinic acid (DMSA) uptake 1 (Week 2) and 5 (Week 6) weeks after partial ureteral obstruction. Paired (weeks 2 and 6) results of absolute ^{99m}Tc DMSA uptake of both the right and left kidneys after bilateral partial ureteral obstruction in rats illustrates that severely obstructed kidneys do not recuperate. Ipsilateral recuperation and compensatory hypertrophy are demonstrated

NAG activity/creatinine ratio ($P < 0.05$) and in the tubular proteinuria/creatinine ratio ($P < 0.01$). Either parameter decreased after week 3 but this was not statistically significant. No significant difference was found for both parameters between weeks 1 and 6. Albuminuria did not change significantly during the study (Table 3). For UPO and BPO, the ROC gave sensitivities of 56%, 73% and specificities of 68%, 72% for the urinary NAG/creatinine ratio, respectively and sensitivities of 83%, 78% and specificities of 72%, 82% for the tubular proteinuria/creatinine ratio, respectively. Considering both UPO and BPO, the area under the curve of the ROC (Figure 3) was 0.796 for tubular proteinuria and 0.633 urinary NAG activity/creatinine ratios ($P = 0.057$).

As regards the individual results, 11 of 45 (25%) animals (UPO and BPO) showed a progressive increase in urinary NAG activity/creatinine ratio, and 7 of them were found to have a significant progressive increase in urinary NAG activity/creatinine ratio (χ^2, $P < 0.01$).

In 13 of the 45 animals (29%), a persistent high tubular proteinuria (>90 mg/g creatinine) was found (UPO and BPO) at week 6. These animals also had a significantly ($P < 0.05$) higher albuminuria [247 mg/g (261.1 mg/g)] than the animals with a tubular proteinuria below 90 mg/g creatinine at week 6 [0 mg/g (99.9 mg/g)]. No significant differences in urinary NAG activity, tubular proteinuria and albuminuria were found in the UPO versus the BPO groups (Table 3). In the sham and control groups, we found no significant (Kruskall-Wallis) difference in urinary NAG activity, tubular proteinuria and albuminuria between weeks 1, 2 and 6 (Table 2).

Correlation between ^{99m}Tc DMSA uptake and tubular proteinuria

In UPO, a positive correlation ($r = 0.78$, $P < 0.01$, $y = 0.0284x + 3.71$) was found between the absolute loss of kidney function at week 2 (^{99m}Tc DMSA uptake of the left minus the right kidney) and the increase in tubular proteinuria from week 1 to week 2.

In 13 of the 45 (UPO and BPO) animals (29%), no decrease in tubular proteinuria was found at week 6 and in these animals a significantly higher loss ($P < 0.01$) of absolute ^{99m}Tc DMSA uptake compared with the controls at week 2 [23% (7.2%) loss absolute ^{99m}Tc DMSA uptake versus 12.5% (6.7%) loss absolute ^{99m}Tc DMSA uptake]. At week 6, the median values of the loss of ^{99m}Tc DMSA uptake [3.59% (4.58%) versus 1.43% (2.61%)] were higher in animals with continuously high tubular proteinuria, but this difference was not statistically significant.

Serum creatinine and urine cultures at week 7

In the UPO, BPO, control population and the sham-operated group, no differences in serum creatinine con-

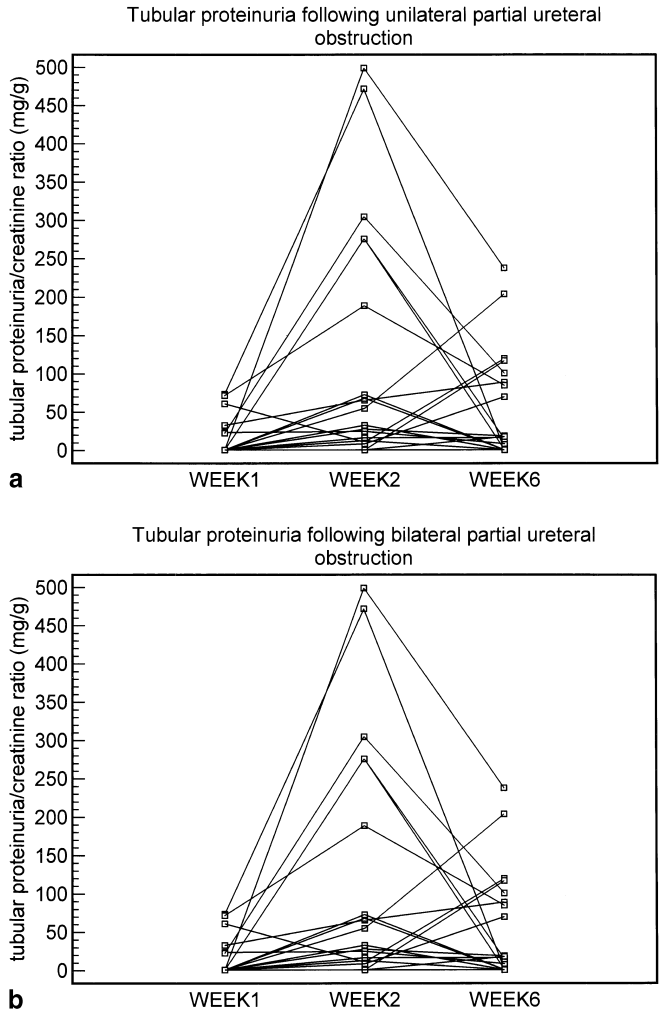

Fig. 2 Tubular proteinuria following partial ureteral obstruction. **a** Following (end week 1) unilateral partial ureteral obstruction ($n = 23$) and **b** bilateral partial ureteral obstruction ($n = 22$), tubular proteinuria increased significantly 1 week postoperatively

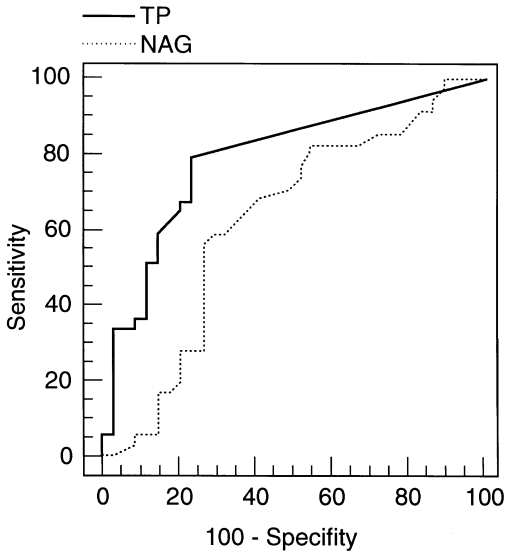

Fig. 3 Tubular proteinuria is superior to the urinary *N*-acetyl-beta-D-glucosaminidase (NAg) activity in the detection of renal tubular damage. Receiver operating curves for urinary NAG activity and tubular proteinuria (TP) following unilateral and bilateral partial ureteral obstruction in rats

centration were found (Kruskal-Wallis). The mean values and standard deviations were for the UPO group ($n = 15$) 0.74 mg/dl ± 0.33 mg/dl, for the BPO group ($n = 13$) 0.72 mg/dl ± 0.11 mg/dl, for the sham-operated group ($n = 7$) 0.70 mg/dl ± 0.19 mg/dl and for the control population ($n = 7$) 0.70 mg/dl ± 0.32 mg/dl. Only one rat (UPO; DMSA uptake obstructed kidney; weeks 1, 6:10.6%, 24%; tubular proteinuria weeks 1, 2, 6:0 mg/g, 896.2 mg/g, 237.5 mg/g) had a high serum creatinine (included in our data). All the urine cultures at week 7 were sterile or had insignificant bacterial growth.

Discussion

Using three different approaches (tubular proteinuria, tubular enzymuria, and ^{99m}Tc DMSA uptake), the existence of a destructive and a steady-state phase in renal function was demonstrated after partial ureteral obstruction [5, 12]. Tubular proteins and urinary NAG activity appear in urine during the destructive phase, and once the steady-state phase is achieved, the concentrations decrease. Therefore, all three parameters give an evaluation of the destructive phase.

Huland et al. [6] described an increase of urinary NAG activity during the 2 weeks following partial obstruction in uninephrectomized rats and thereafter a significant decrease. To obtain a longitudinal study, Huland killed a series of rats every week and compared the results of different weeks (different animals).We confirmed these data in a more clinically relevant setting than Huland's, since no contralateral nephrectomy was performed, and the rats were kept alive for 7 weeks. This might be clinically relevant for the diagnosis of renal colic in children, fetal hydronephrosis and for the decision making in chronic partial ureteral obstruction [3, 15, 19].

In analogy with the findings of Huland et al. [6], tubular proteinuria was found to be a marker of the destructive phase following UPO. A fair correlation ($r = 0.78$) was found following UPO between the increase in tubular proteinuria and the loss of ^{99m}Tc DMSA uptake. Therefore, tubular proteinuria can be considered a marker of renal tubular destruction following UPO.

In our longitudinal setting, we found some animals with persistently elevated concentrations of urinary NAG activity (25%). Hence, the destructive phase is not always followed by a steady-state phase as has been suggested previously [6, 12]. Persistently high concentrations of urinary NAG activity were related to early death. This observation suggests that other noxae were present in these animals, these could have been urinary

tract infections, renal insufficiency or another concomitant disease [2, 4, 7, 20–21].

Continuous elevated tubular proteinuria was not significantly related to early death. Because we measured tubular proteinuria with gel permeation chromatography, glomerular and tubular proteinuria could be distinguished mutually. In glomerular renal disease, tubular proteins and albumin leak through the glomerular membrane [7, 10, 21]. High concentrations of proteins pass through the proximal tubule of the kidney where the reabsorption threshold is quickly exceeded and proteins (tubular as well as glomerular) leak into the urine. In the series presented, elevated tubular proteinuria (>90 mg/g creatinine) at week 6 coincided in 29% of the animals with significant albuminuria. Therefore, persistently high tubular proteinuria after partial ureteral obstruction indicates an evolution to glomerular damage and further renal destruction [7, 21].

The sensitivity and specificity of tubular proteinuria and urinary NAG activity in the diagnosis of renal tubular destruction were similar for the UPO and the BPO groups. No significant differences were found in absolute DMSA uptake or in loss of DMSA uptake of both kidneys between UPO and BPO postoperatively. By analogy, no significant difference was found in tubular proteinuria between the BPO and the UPO group, which suggests that tubular proteinuria correlates with the extent of renal tubular damage rather than with unilateral or bilateral renal tubular damage as such.

Similar to what is reported in other studies [1, 17], we found significant recuperation of ^{99m}Tc DMSA uptake after UPO at week 6. Josephson and Grossman [8] observed mild loss of renal function (kidney weight) in adult rats after UPO, and Koff [14] demonstrated that only in the primary period after partial obstruction is renal damage found and that bouts of high intrapyelic pressure are rather scarce once the pelvis is dilated.

Figure 2 shows ipsilateral recuperation, progressive loss of tubular function, and compensatory hypertrophy and illustrates that below 10%, no ipsilateral recuperation was found. This confirms the data of the De Maeyer [1]. Normal tubular proteinuria was never associated with an absolute DMSA uptake below 10% in our series. If it is encountered, it is the reflection of an end-stage renal atrophy with compensatory contralateral hypertrophy [2]. An absolute DMSA uptake above 10% with elevated tubular proteinuria indicates active renal damage, but ultimately only mild loss in kidney function is expected [8]. An absolute DMSA uptake above 10% with normal tubular proteins means that active renal damage is no longer happening and that no further recuperation is expected. These data need confirmation in an animal model in which de-obstruction is performed to determine the predictive value of tubular proteinuria and the DMSA scintigraphy after partial ureteral obstruction.

Conclusion

A destructive and a steady-state phase in renal function has been demonstrated in adult rats by measuring renal enzymes, tubular proteins and ^{99m}Tc DMSA scintigraphy after UPO, without the performance of a contralateral nephrectomy. The same observation was made after BPO. Tubular proteins and ^{99m}Tc DMSA uptake correlated inversely. Persistent elevated tubular proteinuria was related to severely damaged kidneys on the ^{99m}Tc DMSA scan and significant albuminuria.

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