Renal Impairment in Young Patients with Unilateral Ureteral Lithiasis Obstruction: What Factors can be Responsible?

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In the literature, occurrence of acute kidney injury (AKI) in young patients with unilateral ureteral lithiasic obstruction and without previous renal impairment is not very often reported, and the underlined pathophysiological mechanisms are poorly known; according to some studies, it is a false kidney failure, the increase in serum creatinine being due to absorbtion of obstructed urine in the affected kidney. We have conducted a retro and prospective study in order to identify the possible risk factors that can cause renal function impairment in young patients (18-40 years) with unilateral ureteral lithiasis obstruction and a normal contralateral kidney. Results. From 402 patients included in the study, 20.64% (83 cases) presented with serum creatinine > 1.3 mg/dL. In patients with renal impairment, prevalence of male gender and history of NSAIDS use before admission were significantly higher than in non-AKI group. Serum urea/creatinine ratio, and estimated glomerular filtration rate (MDRD formula) were significantly higher, and respectively lower in AKI group. We found no significant differences between the two groups regarding age, prevalence of urinary tract infection after relief of obstruction, C-reactive protein value, and the duration of hospitalization. Conclusions. AKI in young patients with unilateral ureteral lithiasis obstruction and normal contralateral kidney is not quite a rare finding in our region. NSAIDs use can influence development of AKI, and should be used cautiously even in young patients with renal colic. In our opinion, the presence of AKI in patients with unilateral hydronephrosis demands urgent endourological intervention. Choosing conservative therapy in these patients, especially treatment with NSAIDS may aggravate the renal dysfunction.

Key words: unilateral ureteral obstruction, normal contralateral kidney, acute renal injury, NSAIDS.

Urolithiasis has a major contribution to the world-wide health care burden. According to COE, F.L., *et al.* approximately 12% of the population will develop a urinary calculus during the lifetime, but the incidence depends on geographic location and season [1]. Renal colic is the most common manifestation of urolithiasis and it is responsible for more than 1% of all presentations in emergency departments [2-4].

Non-steroidal anti-inûammatory drugs (NSAIDs) are the first-line treatment for the patients with renal colic, although nephrotoxicity of these drugs represents a major medical concern. In a study of DOUROS, A., *et al.*, NSAIDs were responsible for drug-induced kidney injury in 15% of cases (54% of these patients were already diagnosed with chronic kidney disease – CKD); additionally, NSAIDs seemed to exhibit nephrotoxic properties even in patients with normal baseline renal function [5]. Furthermore, special attention should be considered in patients with previous renal failure, associating different pathologies, such as, diabetes mellitus, hypertension, endocrine disorders etc [6-9].

In healthy young patients without pre-existing conditions of decreased kidney function, renal impairment due to acute unilateral ureteral obstruction is believed to be rare, but a significant number of these cases do have abnormal renal function tests. Unfortunately, little is known regarding the underlined pathophysiological mechanisms.

Experimental part

Material and methods

We have conducted a retro and prospective study in order to identify the possible risk factors that can cause renal function impairment in young patients with unilateral ureteral lithiasis obstruction and a normal contralateral kidney by ultrasound evaluation. We have included all patients aged between 18 and 40 years old admitted to our department for renal colic and acute unilateral ureterohydronephrosis with no history of CKD or other pre-existing conditions that could cause a decreased renal function. In addition, the cases with solitary kidney, history of urolithiasis with previous surgical interventions in the contralateral kidney, and the presence of active urinary tract infection that could complicate the present patient's condition were excluded. According to their serum creatinine levels, the patients were divided in two groups:

- **group A** - with serum creatinine values less than 1.3 mg/dL;
- **group B** - with serum creatinine levels ≥ 1.3 mg/dL (acute kidney injury group)

In all included subjects, complete blood count, renal function tests, C-reactive protein, urine dipstick analysis, urine culture and imaging investigations were carried out. The results were compared between the two groups. Assessment of kidney function was performed by calculating eGFR with the Modification of Diet in Renal Disease (MDRD) formula. Although creatinine-based estimation equations are not usually used for evaluation of kidney function in acute kidney injury (AKI) [10], many investigators often apply these formulas in acute settings for evaluating the effects of various potential nephrotoxic injuries on kidney function (e.g. contrast nephropathy, drug induced nephropathy) [11,12].

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Statistical analysis was conducted using *t-test* for continuous variables and the *Chi-square test* for categorical variables, and *p values of < 0.05* were considered statistically significant.

Results and discussions

A total of 402 patients were included, 319 (79.35%) in **group A** and 83 (20.64%) in **group B**. In **group A**, the mean age was of 31.06 years, and in **group B** of 29.4 years, with no significant difference between the two groups ($p = 0.09102$; $t = 1.69412$). Gender distribution was of 83 (26.01%) males and 236 (73.98%) females in **group A**, while in **group B** there were 72 (86.74%) males and 11 (13.25%) females; the sex ratio was significantly different between the groups ($p < 0.001$; $\chi^2 = 102.529$).

At admission, in **group A** the serum creatinine level was between 0.4 and 1.29 mg/dL (with a mean value of 0.80 mg/dL), while in **group B** it was between 1.31 and 5.4 mg/dL (with a mean value of 1.63 mg/dL) ($p = 0.00001$; $t = 21.68224$). The estimated glomerular filtration rate (eGFR) in group A was between 51.3 and 194.9 mL/min/1.73m^2, mean 105.11 mL/min/1.73m^2, while in group B it was between 12.6 and 70.2 mL/min/1.73m^2, mean 53.89 mL/min/1.73m^2 ($p = 0.00001$; $t = 15.76211$). Regarding the serum urea level, it was between 9-60 mg/dL (with a mean level of 27.38 mg/dL) in **group A**, and in **group B** between 22 and 151 mg/dL (with a mean level of 45.58 mg/dL) ($p = 0.0001$; $t = 12.49513$). In **group A**, the serum urea/creatinine ratio was between 5 and 63.63 (with a mean value of 34.22), and in **group B** between 15.71 and 56.76 (with a mean value of 28.20) ($p = 0.0001$; $t = 12.49513$).

At 48 hours after admission, in **group A** 77 patients (24.13%) had positive urine culture and only 13 (15.66%) in **group B** ($p = 0.098$; $\chi^2 = 2.7227$). The most frequent encountered bacteria was *E.coli* followed by *Klebsiella spp., Proteus* and *Enterococcus spp.* In **group A**, 132 (41.38%) patients had a history of NSAIDs treatment up to 72 hours before admission and 53 (63.85%) in **group B** ($p = 0.000252$; $\chi^2 = 13.3939$). In **group A**, patients used the following NSAIDs: ibuprofen ($n = 10$), ketorolac ($n = 38$), naproxen ($n = 42$), celecoxib ($n = 20$) and dexketoprofen ($n = 22$); in **group B**, patients used: ketorolac ($n = 12$), naproxen ($n = 17$), celecoxib ($n = 11$) and dexketoprofen ($n = 13$).

All demographic features and bioumoral variables (including the inflammatory state) within the two groups are presented in table 1.

In **group A**, the relief of the obstruction was achieved in 152 (47.64%) patients, respectively in 50 (60.24%) in **group B** ($p = 0.04$; $\chi^2 = 4.1774$). In the first 6 hours, the relief of the obstruction was performed in 63 (41.44%) patients in **group A**, and in 26 (52%) in **group B**. In 37 (24.34%) patients from **group A** and in 7 (14%) from **group B**, the intervention was performed between 6 and 12 hour after admission. In 52 (34.21%) cases from **group A** and in 17 (34%) from **group B**, the intervention was performed after more than 12 h after admission. The mean duration time of hospitalization was of 2-18 days in **group A** (with a mean time of 4.176 days), and of 2-11 days in **group B** (with a mean time of 4.12 days) ($p = 0.42$; $t = 0.1935$).

Obstructive AKI is an abrupt decline of renal filtration function secondary to the blockage of the flow of urine in both kidneys or in solitary kidney. Usually, unilateral obstruction in a healthy individual has little influence or no

Table 1
COMPARISON OF DIFFERENT VARIABLES BETWEEN **GROUP A** AND **GROUP B**

	Group A	Group B	*p-value*
No. of patients	319 (79.35%)	83 (20.64%)	*n/a*
Mean age (years)	31.06	29.4	*0.091*
Gender	83 (26.01%) males 236 (73.98%) females	72(86.74%) males 11 (13.25%) females	***< 0.001*** ~~***0.05***~~
Serum creatinine (mg/dL) **Mean value (mg/dL)**	0.4-1.29 0.80	1.31-5.4 1.63	***0.00001***
eGFR (MDRD formula) **(mL/min/1.73m^2)**	51.3-194.9 mean 105.11	12.6-70.2 mean 53.89	***0.00001***
Serum urea (mg/dL) **Mean value (mg/dL)**	9-60 27.38	22-15 45.58	***0.0001***
Positive urine culture	24.13% ($n = 77$)	15.66% ($n = 13$)	*0.098*
NSAIDs use	41.38% ($n = 132$)	63.85% ($n = 53$)	***0.0002***
Urea/creatinine ratio **Mean value**	5-63.63 34.22	15.71-56.76 28.20	***0.0001***
C-reactive protein **> 50 mg/dL**	21.63% ($n = 69$)	25.3% ($n = 21$)	*0.47*

change in measured renal function. According to UCERO, A.C., *et al.* untreated urinary obstruction can lead to tubular atrophy, interstitial fibrosis and inflammation, and ultimately irreversible renal injury; furthermore, kidney recovery may take days to weeks and mortality from AKI is around 50% [13]. MISAKI, T., *et al.* noticed that in an obstructed kidney, tubular cell death appears on day 1 following the obstruction and increases with time. After 2 weeks, tubular dilation and apoptosis peak are observed in both distal tubules and collecting duct throughout the cortex and medulla. Interstitial cells also undergo apoptosis, and is noticed from day 3 after obstruction (it is thought to contribute to the resolution of inflammation, regulation of fibroblast number or microvascular injury) [14].

Although AKI secondary to unilateral obstruction in healthy individuals should not be encountered, in a series of 1923 cases, KIM, H.Y., *et al.* observed an incidence of 5.6% (n = 107), while AL-ANI, A., *et al.* noticed it in 40% (n = 36). The incidence in our study was of 20.64% which stand between these values [15,16]. In addition, a significant increase of the serum creatinine level was observed by KIM, H.Y., *et al.*, with an important creatinine clearance decrease - up to 52.5 *vs.* 92.6 mL/min/1.73m^2 ($p < 0.001$). The decline of creatinine clearance was also showed by AL-ANI, A., *et al.*; in their study, the mean level was 74 ± 29 mL/min/1.73m^2 [15,16]. On the other hand, EL-SHAZLY, M. *et al.* found a creatinine clearance mean value of 95.04 ± 15.41 mL/min/1.73m^2 in a group of 53 patients (all males) with acute unilateral ureteric obstruction due to ureteric stones, normal contralateral kidney, and with a mean serum creatinine level of 178.7 ± 14.83 µmol/L on admission; after the passage of the stones, the clearance mean value was of 94.45 ± 6.37 mL/min/1.73m^2, with no significant differences. The authors concluded that the renal impairment in patients with acute unilateral ureteric obstruction was not a true impairment. Thus, a false increased creatinine was diagnosed, hence a false AKI. A recent publication confirms these data by finding no significant differences of eGFR, measured with Tc-99m, between the moment of admittance in the hospital (when patients had unilateral ureteral obstruction) and the moment of relief of obstruction (urological or after conservative treatment) [17]. In our study the mean level of the serum creatinine (0.80 *vs.* 1.63 mg/dL) and the mean eGFR value (105.11 *vs.* 53.89 mL/min/1.73m^2) were significantly different between the two groups ($p < 0.001$).

We have also noticed a significant increase of the serum urea concentration (a mean value of 27.38 *vs.* 45.58 mg/dL; $p < 0.001$) and serum urea to creatinine ratio (34.22 *vs.* 28.20; $p < 0.001$). According to MORGAN, D.B., *et al.*, urea to creatinine ratio had been long used as a crude method of differentiating between renal failures etiologies [18,19]. In renal function impairment, a urea to creatinine ratio of 40-100 is considered normal or due to a post-renal etiology, while intrarenal and prerenal etiologies are suspected if the ratio is < 40 and > 100, respectively. According to MARSHALL, S., a higher urea to creatinine ratio in the renal impairment group can be explained by the increased tubular reabsorption of urea a decline of urine tubular flow secondary to increased intra-pelvic pressure and decreased glomerular flow rate (consequently to the presence of unilateral ureteral calculi) [20].

There was no significant differences between age in the two groups ($p = 0.09$), because we have included only young patients in order to avoid old individuals with pre-existing CKD or other conditions (e.g. diabetes mellitus or hypertension) that could cause a decreased renal function. In other trials, patients with AKI had a significantly greater age; thus, in AL-ANI, A., *et al.* study, the mean age was of 36.5 *vs.* 42.2 years ($p = 0.02$), while KIM, H.Y., *et al.* reported a greater mean value age of 44.9 *vs.* 58.5 years ($p = 0.001$) [15,16]. On the other hand, in our study, males' patients were significantly more affected by the AKI (26.01% *vs.* 86.74%; $p < 0.001$). From our knowledge, no other authors showed the influence of gender in the development of AKI due to unilateral ureteral lithiasis obstruction.

According to the *European Association of Urology* (EAU) guidelines, pain relief is the first therapeutic step in patients with an acute stone episode [21]. The first line medication is represented by NSAIDs. NSAIDs are effective in patients with acute stone colic, and have better analgesic efficacy than opioids. However, their use is associated with deterioration of renal function. It is known that NSAIDs may further diminish renal function in patients with an obstruction, particularly those with pre-existing renal impairment (undergoing dialysis or not) [22-25]. According to SCHNEIDER, V., *et al.*, this adverse event occurs in approximately 1-5% of cases [26]. The NSAIDs mechanism of action is represented through inhibition of prostaglandin synthesis preventing its effect on arteriolar dilatation. Previous reports of unilateral ureteral obstruction associated with increased creatinine offered several explanations of the phenomena: use of NSAIDs, crystalline nephropathy, immune reaction to crystalluria, dehydration or renin- angiotensin activation [16]. LEE, A., *et al.* showed that diclofenac can affect renal function in patients with pre-existing renal impairment, and it has no functional effect in patients with normal kidney function [27]. AL-ANI, A., *et al.* noticed statistical significance differences between NSAIDs use and AKI in subjects with unilateral ureteral obstruction ($p = 0.03$), but no differences in the type class of NSAIDs used by the patients ($p = 0.11$) [16]. Accordingly to the literature data, we also had a significant higher use of NSAIDs in the group that developed AKI (41.38% *vs.* 63.85%; $p = 0.0002$).

If left untreated, ureteral obstruction can often associate urinary tract infection, which can influence the creatinine clearance and the inflammation test reflects this state. Both KIM, H.Y., *et al.* and AL-ANI, A., *et al.* found a correlation between inflammation and AKI in patients with acute unilateral ureteral obstruction [15,16]. In our study, between the two groups, there were no significant differences regarding the elevated C-reactive protein ($p = 0.47$) and positive urine culture ($p = 0.098$).

In patients with acute unilateral ureteral obstruction, elevated serum creatinine is considered by some as AKI and consequently, urgent intervention is usually performed and conservative medical expulsive therapy (MET) is not recommended. According to EAU guidelines, urgent intervention such as ureteric stenting, percutaneous nephrostomy insertion or urgent ureteroscopy is often recommended in this cases [21]. According to PEARLE, M.S., *et al.*, there are no differences between ureteral stent or percutaneous nephrostomy in urgent decompression of the obstructed kidney [28]. In our series of patients, the presence of AKI influenced the disease management. In the group with AKI (**group B**), the urinary decompression have been performed in a greater number of cases (47.64% *vs.* 60.24%; $p = 0.04$), especially in the first 6 hours after admission (41.44% *vs.* 52%; $p = 0.02$). The presence of AKI and the therapeutic management did not influence significantly the hospitalization time (mean time of 4.176 *vs.* 4.12 days; $p = 0.42$).

A very odd, rare, but fascinating phenomenon that has been proposed for more than half a century is reflex anuria. HAYASHI, K., *et al.* described this situations when there was unilateral ureteric obstruction, and the contralateral

kidney was expected to retain its normal function [29]. HOU, W., *et al.* explained reflex anuria as a cessation of urine production caused by stimuli on kidney, ureter or other organs, through a mechanism of reflex spasm of intrarenal arterioles or ureters, leading to acute renal injury [30]. It is rather a functional than parenchymal disease. The authors suggested that reflex anuria is a diagnosis of exclusion, considered only after ruling out common and tangible etiologies such as ureteral calculi, acute tubular necrosis, renal vascular occlusion, hypovolemia, infection etc. If the diagnosis has been established, treatment plan should be directed toward the mechanisms more than to the causative factors [31]. Because it has never been presented in large series of patients, and there is a lack of systematic evidence some authors like HIPSLEY, P.L. or SIROTA, J.H., *et al.* denied the existence of reflex anuria [32,33].

Conclusions

With an incidence of 20.64%, AKI in young patients with unilateral ureteral lithiasis obstruction and apparently normal contralateral kidney (without pre-existing CKD) is not quite a rare finding in our region. Factors like male gender or NSAIDs use can influence development of AKI, and should be used cautiously even in young patients with renal colic. The presence of AKI in young patients with unilateral renal colic and unilateral hydronephrosis may worsen prognosis and further complicate evolution of the disease unless emergency endourological intervention is performed. Choosing conservative therapy in these patients, especially treatment with NSAIDS may aggravate the renal dysfunction.

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