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Improving The Microenvironment Activity of Ureteral Stones by The Preoperative Placement of Ureteral DJ Stent Has Significant Benefits for The Treatment

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Ureteral stones; DJ stents; Preoperative DJ stent placement; Benefits for ureteral stones treatment

1. Abstract

1.1. Introduction

Ureter stones are originally formed and exit in the renal pelvis of the kidney and subsequently moved into the remainder of the urinary collecting system, including the proximal, middle, and distal regions of the ureter. Ureteral JJ stent, which is also known as double J stent (DJS) has many urological functions which include keeping the ureter patent and ensuring resolution of the complex of edema and injury.

1.2. Aims

We aimed to scrutinize the contribution of preoperative DJ stent for small and medium-size ureteral stones in terms of operative time, intraoperative complications, reoperative risk, and requisites for postoperative DJ stent. We reviewed, the medical register of our Hillel Yaffe Medical Center (HYMC) from April 2018 up to September 2019 for ureteroscopic procedures due to ureteral stones.

1.3. Results

Patients were classified into two groups i.e. whether they had ureteral stent before the operation (Group A) or had not gone through this procedure (Group B). Median operating time, postoperative stenting, period of postoperative stent, rate of complications, reoperative procedure were assessed. Our analysis of the variations between groups A and B have shown that preoperative DJ stent placement was associated with a higher stone-free rate (SFR), decreased reoperative rates, decreased perioperative complications, and decreased requisite for postoperative ureteral stenting, but no influence was observed on the operative times.

1.4. Conclusion

Our results may lead to the conclusion that using the DJS prior to ureteroscopic procedures may improve the microenvironment activity of ureteral stones, which subsequently results of having significant benefits for the treatment.

2. Introduction

Stone formation in urinary tract systems is an advanced stage and has a significant effect on the severity of urolithiasis, and may affect the welfare of patients [1-3]. Urolithiasis is a condition that is developed when the stones are formed and exit in the renal pelvis of the kidney and move into the remainder of the urinary collecting system, which includes the ureters (proximal, middle, and distal regions), bladder, and urethra. Not rarely, urolithiasis can be managed conservatively in which no active stone removal policy is provided, other than analgesic and anti-emetic medications for four to six weeks [1,4,5]; However, stones that are associated with obstruction, renal failure, and multiple infections, require further increasingly critical interventions [1,2]. Urolithiasis is a prevalent disease causing a large number of admissions to the emergency room (ER) in hospitals [6]. Epidemiological studies have shown that the prevalence of urolithiasis is about 12% of the world population [7], with approximately 1 out of 11 people in the United States of America (USA) affected and is known to be varied in the different ethnic groups in the United States [8]. It is estimated to cost the USA health care system more than US$5 billion and is responsible for approximately 1 million ER visits annually [8]. Its prevalence is rising and primarily affects the working-age populations and people living at low socioeconomic conditions. It is also known that the prevalence of this disease is higher in men than

women, 10.6% vs. 7.1%, respectively, which may be attributed to different lifestyle, hormonal, and genetic structures factors [9, 10]. Recent studies have reported that the prevalence of urolithiasis has been increasing in the past few decades in both developed and developing countries. This growing trend is believed to be related to sedentary lifestyle including lack of physical activity, specific dietary habits [11-13] and global warming [14]. The etiology of kidney stone is multifactorial, and common risk factors for stone formation include poor oral fluid intake, high animal-derived protein intake, high oxalate intake (found in foods such as beans, beer, berries, coffee, chocolate, some nuts, some teas, soda, spinach, potatoes), and high salt intake [11-13]. Previously, it was suggested that stone formation in kidneys is a complex process and the interactions between environmental factors with underlying genetic factors may cause stone disease [9], while an innovative study has reported a list of genetic defects, which lead to stone formation [10].

Oral hydration is recommended at a rate that produces approximately 2.5 liters (L) of urine per day, and acceptable choices for fluids include water, coffee, tea, beer, and low sugar fruit juices except for tomato (high sodium content), grapefruit, and cranberry (high oxalate content). Consumption of citrate helps to prevent stone formation as it inhibits crystal aggregation by forming complexes with calcium salts within the urine [15,16]. It was reported that patients with a background medical condition such as chronic kidney disease, hypertension, gout, diabetes mellitus, hyperlipidemia, obesity, endocrine disorders, and malignancies are at higher risk for the development of kidney stones. Previous studies have shown that metabolic diseases including obesity, hyperlipidemia, and type 2 diabetes mellitus (T2DM) have a strong predilection for calcium oxalate and uric acid stones formation [17,18]. Such an observation could be explained by the effect of the metabolic diseases induced systemic inflammation status which could affect the kidney function as well the entire urinary tract system. Ureteral JJ stent, which also know by double J stent (DJS) has many urological functions, and is among the basic and commonly used tools in urology in many procedures since its first introduction in 1967 by Zimskind et al. [19]. These stents keep the ureter patent and ensure resolution of any edema and local injury/inflammation. Hence, it is considered as an effective method in the management of patients with ureteric calculi, ureteric stricture, retroperitoneal tumors, or fibrosis, ureteropelvic junction obstruction or any iatrogenic ureteric injury. The ureters may become blocked because of several conditions, including Kidney stones, tumors, blood clots, postoperative swelling, and infection. DJS is the procedure in which a thin, soft, hollow, flexible plastic tube is deployed temporarily in the ureter to help urine drain from the kidneys into the bladder in the case of blockage. A ureteral stent may also be placed during or after urinary tract surgery to provide a mold around it, in which healing can occur, to divert urine away from injured areas with leakage, to manipulate kidney stones or prevent stones from moving prior to treatment, or to make the ureters more easily identifiable during surgical procedures. Its main historical designation was to help the internal drainage for upper urinary tract obstruction. Beyond this role, nowadays it is widely utilized as accompanying tool for drainage either before or after endoscopic procedures in the upper urinary tract system [19-22]. The DJS may remain in the patients from days to weeks and even months, depending on the situation. Several previous works have reported the success in treating ureteral stones, when previous attempts to access the ureter have failed by decongesting the ureter prior the operation, [23]. The role of DJ stent as passive dilator of the ureter in children's patients with previously failed ureteroscopic attempts was repeatedly stressed. Nevertheless, indwelling stents colonization by host of microorganism may jeopardize the leverage of preoperative stent upon ureteroscopy and its outcomes [24]. Most of the ER renal colic visits are due to small and medium size stones [8]. These stones can be treated conservatively by active medical expulsive (MET) therapies or alternatively by means of early ureteroscopy [5]. The role of preoperative stenting in this group of patients is unequivocal. Most of the studies that reviewed the efficacy of preoperative stenting neither differentiated renal stones from ureteral stones, nor high volume stones from small volume stones. Here, we aimed to scrutinize the contribution of preoperative DJ stent for small and medium size ureteral stones in term of operative time, intraoperative complications, re-operative risk and requisites for postoperative DJ stent. Our study was based on retrospective analysis of patients' data, and our results have shown that preoperative DJ stent placement was significantly associated with higher stone-free rate (SFR), decreased re-operative rates, decreased perioperative complications, and decreased requisite for postoperative ureteral stenting, but no influence was observed on the operative times.

3. Methods

We retrospectively reviewed the medical register of our Hillel Yaffe Medical Center (HYMC) from April 2018 up to September 2019 for ureteroscopic procedures due ureteral stones. We excluded patients with renal stones, high volume stones (>12 mm), multiple ureteral stones (>2 stones), bilateral stones, white ureteroscopy, ureteroscopy in pregnant women and children. The study protocol was approved by the Hillel Yaffe ethical committee (IRB No. 0071-20HYMC), and written informed consent was waived. The eligible patients were classified into two groups depending on whether they had ureteral stent before the operation (Group A) or they had not gone through this procedure (Group B). The indications for ureteral stent insertion in the first group (group A) were as follow: intractable pain, blood creatinine>1.4 mg/dl, obstruction with signs of infection, unsuccessful prior ureteral access attempt, and patients who were stented in other institutions and then were referred to our institution for ureteroscopy. For each group we ex-

tracted data regarding patients' characteristics (age, gender, body mass index (BMI)), stone features (size, location in the ureteral, density and laterality), operating time in minutes, number of ureteroscopic procedures, operative complications, stone free rate and postoperative DJ stenting (precluding 24h ureteral catheter). For stented patients (group A) we calculated the median prestenting period (in days). For comparative purposes, each group (A and B) was subsequently subdivided into 4 subgroups according to their stone size and location in the ureteral. These groups are as follows: 1. A1/B1-stones > 5 mm in the middle and upper ureter; 2. A2/ B2 stones > 5 mm in the lower ureter; 3. A3/B3 stones ≤ 5 mm in the middle and upper ureter; and 4. A4/ B4 stones ≤ 5 mm in the lower ureter). The goal of this subdivision was to isolate contributing factors and improve results precision. All the ureteroscopic procedures were done by expert urologists using semi-rigid ureteroscopes, only (Storz 6.5 FR and Storz 8.9 FR); the procedure involves the passage of a small telescope, called a ureteroscope, through the urethra and bladder and up the ureter to the point where the stone is located. Ureteral pigtail DJ stents were all in the same diameter (6 FR) and were previously inserted in the operating room using cystoscopy. Ureteral stents are placed temporarily into the ureter which is the tube that drains urine from the kidney into the bladder. Upper ureter stones that migrated proximally into the collecting system were cleared using flexible ureteroscope, but these procedures were subsequently excluded from the study to reduce confounding factors that may affect the results. Laser fibers used includes 365µm and 500µm holmium laser fibers and all stone fragments were retrieved using tipless basket. The objective of the ureteroscopic treatment was to clear all retrievable residual fragments > 2 mm. At the end of each procedure the implantation of postoperative drainage tube (DJ stent, DJ stent with external wire or Ureteral catheter) or finishing the operation without ensuing ureteral catheterization was left to the discretion of the operator. The decision of postoperative ureteral catheterization relies on several technical intraoperative factors like operating time, difficult stone fragmentation or retrieval, ureteral wall trauma, ureteral orifice status and the surgeon assessment for ureteral diameter and clearance. Most patients were followed 3-6 weeks post the operation and were submitted to our clinic with postoperative imaging (NCCT, urinary abdominal X ray or urinary US), and blood tests to assess their stone clearance status. We compared the results of each group in accordance with the aforementioned parameters and evaluated the efficacy of preoperative stenting in terms of operating time, number of ureteroscopic procedures, complications, hospital stay, stone free rate and the requisite for postoperative DJ stenting.

4. Statistical Analysis

Quantitative data are expressed as mean ± standard deviation (SD), range, or number and percentage. We used the analysis of independent t-test and the Chi-square test to compare patients' data in groups A and B. The data were analyzed with the SPSS (Chicago, USA), p value<0.05 was considered significant.

5. Results

In the current study we retrospectively evaluated and compared eligible consecutive patients, who presented to the ER with urolithiasis, with one cohort being treated with upstream DJ stent before the ureteroscopic procedures, while the other being conservatively treated towards the ureteroscopy. Out of 475 ureteroscopic procedures performed in the study period, and complied with our selection criteria, only 318 procedures done for 290 different patients were eligible for recruitment in the study. The prestented group included 83 procedures done for 80 different patients and they were assigned in four subgroups, A1-4, and each contained 37, 15, 11 and 20 patients, respectively. The non-prestented group included 235 procedures for 210 different patients and they were assigned in four subgroups, B1-4, and each contained 66, 43, 49 and 77 patients, respectively. The patient's characteristics are illustrated in Table 1.

Data analysis has shown a significantly (P<0.005) larger stones size (6.53 + 2.30,) in the prestented cohort when comparing relative to the non-stented cohort (5.72 + 2.24) as shown in Table 1 and Figure 1A. Moreover, the upstream stenting policy showed significantly lower need for stenting at the end of ureteroscopy, with values of 27.7% and 54%, respectively, P<0.001 (Table 1 and Figure 1B). In addition, the postoperative stenting time was significantly shorter in the prestented cohort (11.7 vs. 16.4 days, P<0.001, respectively) (Table 1 and Figure 1C). Finally, of the need for recurrent "rescue" ureteroscopy was again significantly higher in the non-stented group, being 7.6% vs. 2.4%, P<0.03(Table 1 and Figure 1D). The remaining indices showed no significant differences between the two cohorts.

Accounting for confounding variables we assessed the effect of age, sex, BMI and race of the patients in the two studied cohorts i.e., presented and non-stented. We found no significant differences between these categories in the two groups (Table 2). We then tested the stones specification in the two groups, according to their size and location in each studied group category. Size was divided into two groups: small size stones ≤ 5 mm and medium size stones 6-12 mm. Location was divided into 3 categories: proximal, middle and distal ureter. Stones features in correspondence to size and location are illustrated in Table 2. We proved a significant difference between the median stone burdens in the two groups, being higher in the stented group (6.52 + 2.3 vs. 5.72 + 2.24, P<0.005). Similarly, the observed stone density was significantly highest in the presented group (861 + 342 vs. 745 + 348, P<0.008, respectively). The other characteristics including Laterality, stone location and the number of stones showed no significant differences.

Table 1. Patient characteristics of the prestented and non-stented cohorts including mean stone size, stone location, median operating time, postoperative stenting, period of postoperayive stent, rate of complications, reoperative procedure and stone clearance rate after first URS. Group (A) Presents Presented cohort and its subgroups including; A1 – stones > 5 mm in middle and upper ureter: A2- stones > 5 mm in lower ureter: A3 – stones ≤ 5 mm in middle and upper ureter: A4 – stones ≤ 5 mm in lower ureter. GROUP (B) presents the non-stented cohort and its subgroups including; B1 – stones > 5 mm in middle and upper ureter: B2 – stones > 5 mm in lower ureter: B3 – stones ≤ 5 mm in middle and upper ureter: B4 - stones ≤ 5 mm in lower ureter.

	Mean stone size (± SD)	**Stone location**	**Median operating time in minutes (±SD)**	**Postoperative stenting**	**Period of postoperative stent (days)**	**Rate of complications**	**Reoperative procedure**	**Stone clearance rate after first URS**
Prestented								
A1 (37 patients)	8.27 ± 1.38	Proximal- 27 Middle- 10 Distal - 0	16.3 ± 7.8	16/37 (43%)	14	2/37 (5.4%)	2/37 (5.4%)	95%
A2 (15 patients)	7.4 ± 1.4	Proximal- 0 Middle- 0 Distal – 15	20.2 ± 8.2	4/15 (27%)	13	1/15 (6.6%)	0/15 (0%)	95%
A3 (11 patients)	4.09 ± 0.83	Proximal- 8 Middle- 3 Distal – 0	13.2 ± 4.3	2/11 (20%)	11	1/11 (9%)	0/11 (0%)	91%
A4 (20 patients)	4.0 ± 0.91	Proximal- 0 Middle- 0 Distal - 20	12.1 ± 2.8	1/20 (6%)	7	0/20 (0%)	0/20 (0%)	100%
Group A	**6.53 ± 2.3**	**Proximal- 35 Middle- 13 Distal - 35**	**15.5** ± 7.03	**23/83 (27.7%)**	**11.7**	**4/83 (4.83%)**	**2/83 (2.4%)**	**95%**
Non prestented								
B1 (66 patients)	7.95 ± 1.53	Proximal- 45 Middle- 21 Distal – 0	18.9 ± 10.5	53/66 (80%)	19	11/66 (16.66%)	12/66 (21.1%)	76%
B2 (43 patients)	7.41 ± 1.49	Proximal- 0 Middle- 0 Distal – 43	15.6 ± 8.5	22/43 (52%)	18	6/43 (13.9%)	2/43 (4.65%)	95%
B3 (49 patients)	4.166 ± 0.93	Proximal- 37 Middle- 12 Distal – 0	15.0 ± 6.5	28/49 (58%)	20	5/49 (10.2%)	5/49 (10.2%)	86%
B4 (77 patients)	3.83 ± 0.81	Proximal- 0 Middle- 0 Distal - 77	14.45 ± 7.7	24/77 (31%)	11	8/77 (10.3%)	1/77 (1.2%)	98%
Group B	**5.72 ± 2.24**	**Proximal- 82 Middle- 33 Distal –120**	**16.01 ± 8.69**	**127/235 (54 %)**	**16.4**	**24/235 (11 %)**	**18/235 (7.6%)**	**89%**
	P value 0.00589	**P value 0.3699**	**P value 0.8902**	**P value <0.001**	**P value 0.00106**	**P value 0.1254**	**P value 0.0332**	**P value 0.125**

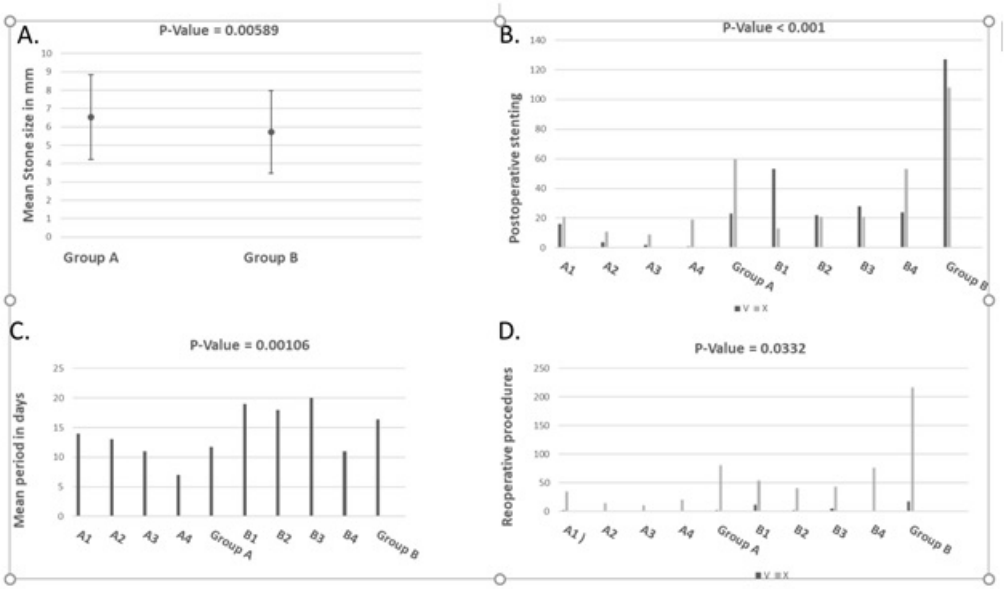

Figure 1. Comparison of the Patient characteristics, which were, significantly different between groups A and B. P value of the comparison is presented on the top of each characteristics. **A.** Meanof stone size in mm (Y-axis) including the standard error in each of groups A and B as shown in X-axis. B. number of patients which went through of postoperative stenting (V) of total tested patients (X) in each group of A and B and each of its subgroups A1, A2 and A3, and B1, B2 and B3, respectively (X-axis). Y-axis present number of stenting. C. The mean period in days (Y- axis) of each group of A and B and each of its subgroups (X-axis). D. The number of patients which went through the reoperative procedure success rate (V) of total tested patients (X) in each group of A and B and each of its subgroups.

Table 2. Patient characteristics including median age, sex, median BMI and race in groups A andB, and number of patients per stones features including its laterality, location, stone density and number of stones per patients. Stone laterality is designed based on left or right, while stone locationis designed based on proximal, middle, and distal. Location was divided into 3 categories: proximal,middle, and distal of the ureter. Stone density with standard error for each group is presented, and number of patients per each category of number of stones i.e., one or two stone are presented. P value of the statistical analysis of comparing findings between group A and B per Patient characteristics and stones features are presented.

Patient characteristics	**Prestented cohort n=83**	**Non stented cohort n= 235**	**P value**
Median Age	49.12 ± 14.3	46.4 ± 13	0.118
Sex	Male- 60 (72%) Female- 23 (28%)	Male – 176 (75%) Female – 69 (25%)	0.1992
Median BMI	28.1± 5.12	27.4 ± 4.63	0.272
Race	Jews – 49 (59%) Arabs – 33 (40%) Others – 1 (1%)	Jews -146 (62%) Arabs – 80 (34%) Others- 9 (4%)	0.38

Stone characteristics			
Laterality	Left- 45 (54%) Right – 38 (46%)	Left- 115 (49%) Right – 120 (51%)	0.309
Median Stone burden	6.53 ± 2.3	5.72 ± 2.24	0.00589
Stone location	**Proximal- 35 (42%)** **Middle- 13 (16%)** **Distal - 35 (42%)**	**Proximal- 82 (35%)** **Middle- 33 (14%)** **Distal –120 (51%)**	0.369
Stone density	861 ± 342	745± 348	0.008
Number of stones	One stone-78 (94%) Two stones – 5 (6%)	One stone- 224 (95%) Two stones – 11 (5%)	0.573

6. Discussion

The formation of kidney stones is a major human health problem. Despite ample studies, the precise processes involved in minerals precipitation and dissolution leading to stone formation remains poorly elucidated and, hence, definitive actions to prevent stones occurrence is yet to be clarified. Ureter stones are originally formed in the kidney, exiting through the pelvis, and subsequently moving to the different parts of the urinary collecting system: the proximal, middle and distal segments of the ureter [3,7,25]. Virtually, many cases with ureter stones can be managed conservatively with watchful waiting, in which no active intervention to remove the stone is employed for four to six weeks, while just prescribing analgesic and anti-emetic medications [4, 26] to improve the patient's welfare. As a role, the choice of treatment for a ureter stone depends on both- the stones size and the severity of pain caused. Therefore, stones that are associated with unrelenting obstruction, renal failure, and recurrent infections, require active interventions in the mode of stenting [6, 26]. It is believed that the interactions between the mechanical stretching effect of the ureter stones, and the normal cells of the host's ureter may activate these cells including fibroblasts, endothelial cells, pericytes, adipocytes, and immune cells, affecting extracellular vesicles, the extracellular matrix (ECM), and cytokines surrounding these stones [27]. The complex interactions of the ureter stones with normal cells of the ureter tissue and the other inflammatory players are known as the ureter stone microenvironment (USME). The stented group represents a "facilitated ureteroscopy" model in which the decon-

gestive effect of stenting enhances a positive biological behavior of the normal cells surrounding the stone and components of the USME, that culminate in a favorable course: higher stone-free rate (SFR), decreased re-operative need, decreased perioperative complications and decreased requisite for postoperative ureteral stenting. D J stent (DJS) is the procedure to place a thin, flexible plastic tube that is temporarily in the ureter to help urine drain from the kidneys into the bladder in the case of blockage, as shown in Figure 1. Since its introduction in 1967 by Zimskind et al. [19], DJ stent is commonly used in various urological procedures [20-22, 28]. The incidence of complications related to stent increases with the duration of the stent; hence, it is important that it should be removed or replaced on time [29]. Globally, kidney stone disease prevalence and recurrence rates are increasing [7], with limited options of effective drugs. Urolithiasis affects about 12% of the world population at some stage in their lifetime [14]. It affects all ages, sexes, and races but occurs more frequently in men than in women within the age of 20–49 years [30]. In this report, we retrospectively investigated the role of the upstream facilitated ureteroscopy approach by implanting flexible ureteral stents in patients presenting with ureteral stones, in comparison with the prevalent, standard conservative approach free from active stenting. studied and compared several characteristics of patients, who have developed stones in their ureter, while one cohort has received DJ stent before the ureteroscopic procedures, while the second cohort did not perform this procedure. Our results proved that the facilitated approach with DJ stent placement prior to the ureteroscopic procedures, is significantly associated with higher SFR, decreased re- operative needs, decreased perioperative complications and decreased requisite for postoperative ureteral stenting, with no influence on total operative times.

We believe that the acute mechanical anti-congestive effect of the DJS in the ureter, this obviously will stop the draining of the urine from the kidney to bladder through the ureter, and subsequently eliminate the continues washing and cleaning of the ureter stone microenvironment, which subsequently will might potentially result in improving the microenvironment activity of ureteral stones, including the immune system activity by increasing the present, not only the nephrolithiasis and microphages but also the different cytokines and chemokines and nitric oxide (NO) and other chemicals, that are produced by the host cells, which may decrease the apoptosis of the urothelium, and, subsequently reduce the adherence and attachment of the stones with the lining cells, and results of releasing and isolate the stone from the surrounding environments, and making it easier to remove the blocking stone, which is translated to higher stone-free rate (SFR),It is speculated and expected that by improving the USME, this will produce new healthy fibroblasts and endothelial cells, which, eventually will significantly benefits the patients by higher SFR, decreased re-operative rates, decreased perioperative complications and decreased requisite for postoperative ureteral stenting.

Previously, it was reported that the attachment of grown crystals with the renal tubule lining of epithelial cells is termed as crystal retention or crystal-cell interaction [31, 32]. In individuals with hyperoxaluria, renal tubular epithelial cells were injured due to exposure to high oxalate concentrations or sharp calcium oxalate monohydrate (COM) crystals [33, 34]. Crystal-cell interaction results in the movement of crystals from basolateral side of cells to the basement membrane [33]. Then, crystals could be taken into cells and anchored to the basement membrane of the kidneys [35]. The interaction of COM crystals with the surface of renal epithelial cells could be a critical initiating event in nephrolithiasis. An increased retention force between the crystal and injured renal tubule epithelium cells promotes CaOx crystallization [36]. Most of the crystals attached to epithelial cells are thought to be digested by macrophages and/or lysosomes inside cells and then discharged with urine [35]. Following renal tubular cell injury, cellular degradation produces numerous membrane vesicles which are nucleators of calcium crystals as supported by in vitro and in vivo studies [31]. Injured cells release substances like renal prothrombin fragment-1 or other anionic proteins which induce COM crystal agglomeration [37]. Reactive oxygen species is thought to be one of the factors involved in renal cell injury [38]. A study on animal models also revealed that the administration of high concentrations of CaOx crystals or oxalate ions appears to be toxic causing renal tubular cell damage [31]. It has been suggested that oxalate increases the availability of free radicals by inhibiting enzymes responsible for their degradation. For instance, reactive oxygen species can damage the mitochondrial membrane and reduce its transmembrane potential. These events are known features of early process in apoptotic pathways [39]. Finally, our findings support the role of early active approach, the facilitated ureteroscopy approach in which ureteral DJ stents implantation in patients suffering from ureterolithiasis should be implemented early in the disease course for some better outcomes. Furthermore, it will be important to assess the microenvironment activity profiles of the ureter stones before and after inserting the DJ stent to confirm our findings in future studies.

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