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Urolithiasis Updated Management Guidelines in Lower Ureters

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Abstract:

Background: Urinary calculi are one of the most common diseases of the urinary tract. The prevalence rate has gradually increasedto 20% in recent decade. Medical expulsive therapy (MET) has been discussed as a conservative treatment option in the management of distal ureteral stones. Medical management therapy including alpha-blockers, calcium channel blockers and phosphodiestrase5 (PDE5) inhibitors have been described. Stone passage through the ureter is dependent on stone diameter and ureteral condition. In addition to ureteral spasm, edema is an important factor in arresting ureteral stone passage. Alpha-blockers can inhibit ureteral muscle contraction, reduce basal muscle tone and reduce peristaltic rate. The alpha-1 adrenergic blockers are most common used agents for MET. Silodosin may increase the rate of stone expulsion rate and decrease the expulsion time.

Key words: Urolithiasis, Silodosin, Tadalafil.

Urolithiasis

Urolithiasis is one of the most common diseases of the urinary tract. The lifetime prevalence of urinary stones is around 1% to 15%, and the peak age of incidence is at 30 years. Men are affected 2 to 3 times more often than women **(1).** Ureteral stones account for 20% of the calculi in urolithiasis and about 70% of ureteral stones are present in the distal third of the ureter at the time of presentation **(2).**

Ureteral stones induce ureteral spasms that interfere with stone expulsion. Thus, reducing these spasms, while maintaining normal peristaltic activity can facilitate stone expulsion. Medical expulsive therapy (MET), in particular a-blockers, has been recommended as supportive medication for patients with ureteral stones and purported to reduce healthcare costs by facilitating stone passage and decreasing the need for interventional procedures **(3).**

Alpha blockers used as medical expulsive therapy (MET) have replaced minimally invasive procedures as the first line of management for small ureteric stones **(4)**.

A previous study conducted by **Yucel** has identified nitrergic fibers in the distal ureter and demonstrated a relaxant effect of nitric oxide pathway on ureteral smooth muscle**.** Since then, investigators focus on how treatment of the nitric oxide pathway can be effectively implemented in clinical practice until phosphodiesterase-5 inhibitors (PDE5Is) emerged. **(5)**

Recently, other investigators **(6)** have assessed the effect of PDE5Is on spontaneous stone passage in patients with expectantly managed ureteral stones. The results of these studies showed a positive benefit with PDE5Is.

Anatomy of the Ureter

The ureters are a pair of thick walled, narrow, distensible, cylindrical muscular tubes whose peristaltic contraction conveys the urine from the renal pelvis to the urinary bladder. In the adult, the ureters are usually 25-30 cm (10-12 inches) long and around 3-4 mm (0.12-0.16 inches) in diameter. **(7)**

1-Macroscopically:

The ureter is entirely a retroperitoneal structure. It is divided into two almost equal abdominal and pelvic portions. The abdominal ureter extends from renal pelvis to the iliac vessels and the pelvic ureter extends from the iliac vessels to the bladder. The abdominal ureter consists of lumbar and iliac parts and the pelvic ureter consists of a longer parietal and a shorter intravesical division **(7).**

The ureter enters the lesser pelvis (true pelvis) by crossing anterior to either the end of the common, or the beginning of the external iliac vessels **(7).**

In the male, as it descends anteromedially, the ureter iscrossed above and in front and from lateral to medial, by theductus deferens just before the ureter enters the bladder.Thereafter the ureter passes in front of and slightly above theupper end of the seminal vesicle and finally enters the bladderwall **(8).**

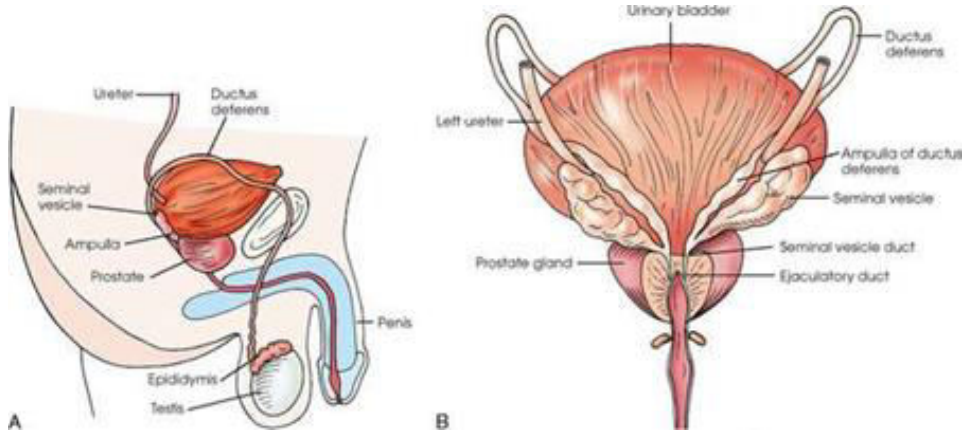

Fig. (1): The lower ureters, urinary bladder, prostate and internal genitalia in male (A: lateral view and B: posterior view) **(8).**

In the female, the pelvic part of the ureter at first has the same general relations as in the male. The ureter is situated behind and medial to the ovarian vessels as they cross the pelvic brim and enter the suspensory ligaments. Though where the ureter lies anterior to the internal iliac artery, it is situated immediately behind the ovary and here forms the posteriorboundary of the ovarian fossa. In its later forward and medial course to the bladder, it has important relations to the uterine artery, the cervix of the uterus and the fornices of the vagina **(9)**.

The ureters pierce the bladder wall obliquely (termed the uretrovesical junction and travel in this orientation for 1.5 to 2.0 cm within the bladder wall to terminate in the bladder lumen as ureteral orifices**. (7).**

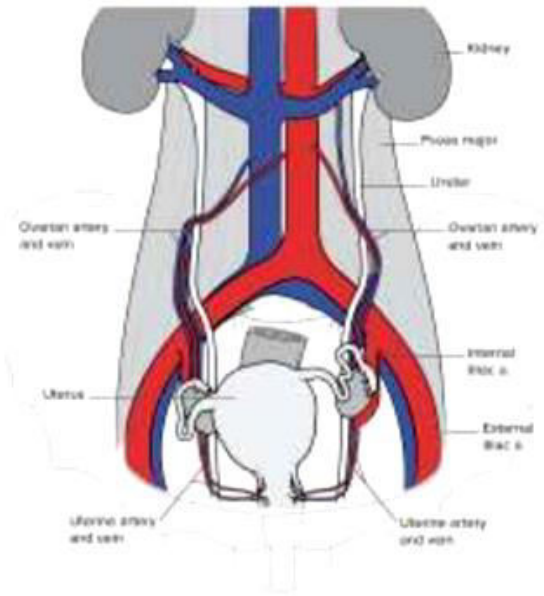

Fig. (2): Relations of the ovarian vessels and the uterine artery to the ureter during oophorectomy or hysterectomy **(9)**.

2- Microscopically:

the ureter is lined by transitional epithelium that is capable of responding to stretches in the ureters. The transitional epithelium may appear as columnar epithelia when relaxed, and squamous epithelia when distended. Deep to the epithelial layer is the lamina propria that is made up of loose-to-dense connective tissue with many elastic fibers interspersed with blood vessels, veins and lymphatics. The thickest layer of the ureter is the muscularis,which is composed of smooth muscles oriented in an inner longitudinal layer of muscle and an outer circular or spiral layer of muscle. The outer portion of the ureter is the adventitia, a protective fibrous layer that harbors the vascular supply. The wall of the ureter becoming gradually thicker as proximity to the bladder and has an additional longitudinal smooth muscle layer in the distal one-third to assist with peristalsis. The ureter passes through the wall of the bladder obliquely, forming a valve that prevents the backflow of urine **(10).**

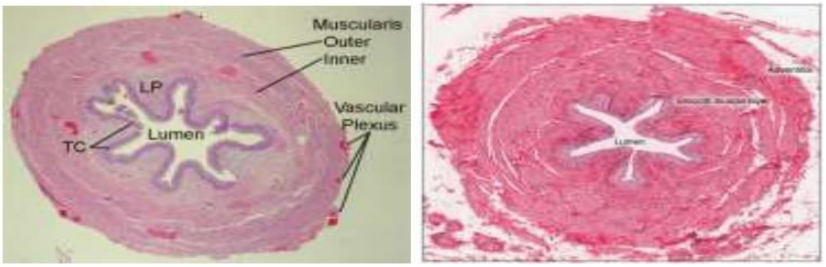

Fig. (3): Histology of the ureter. LP = lamina propria; TC = transitional cell epithelium **(10).**

3- Surgically: the ureter can be divided into upper, middle, and lower segments. The upper ureter extends from the ureteropelvic junction (renal pelvis) to the upper border of the sacrum, the middle ureter comprises the segment from the upper to the lower border of the sacrum, and the lower ureter (distal or pelvic ureter) extends from the lower border of the sacrum to its orifice in the bladder **(11)**.

4- Endoscopically: a normal ureter is relatively uniform in caliber and easily distensible; however, there are three naturally occurring relatively narrow sites within the lumen that are recognizable endoscopically: the ureteropelvic junction, the pelvic brim region (the crossing of the ureter over the iliac vessels) and the ureterovesical junction. These three narrowing sites are clinically

significant because they are common locations for urinary calculi to become trapped and obstructing during passage. There is a true physical restriction of the ureter as it makes the intramural passage through the bladder wall to the ureteral orifice **(12)**.

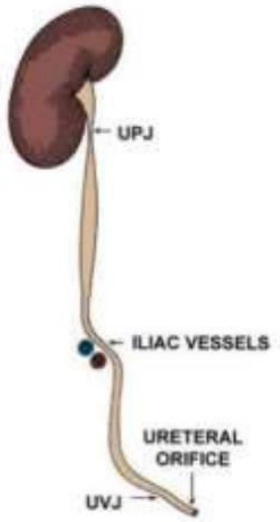

Fig. (4): The ureter demonstrating sites of normal functional or anatomic narrowing at the ureteropelvic junction (UPJ), the iliac vessels, and the ureterovesical junction (UVJ). Note also the anterior displacement andangulation of the ureter, which occurs over the iliac vessels **(12)**.

Ureteric Calculi

Epidemiology of urolithiasis

Urolithiasis is one of the urinary tract's most common diseases. The urinary stones' lifetime prevalence is around 1% to 15%. Ureteral stones account for 20% of urolithiasis calculus and about 70% of ureteral stones are found in the distal third of ureter at time of presentation. **(11).**

Generally speaking, it is more common in men than women. Male to female ratio is: 1.2 to 2.7 **(11).** Geography often influences the occurrence of urolithiasis and the form of calculus in a specific area. There is a higher incidence of urolithiasis in industrialized countries and a marked prevalence of calcium oxalate major component on renal calculus compared to other countries **(11).**

Types and composition of ureteral stones:

A- ***Types of calculi:***

1- Primary ureteral calculi

The normal ureter walls are smooth and the flow of urine is normally fast; hence, stones do not typically develop in the ureter except for pre-existing ureteral disease. A calculus might develop just above the lesion, but the possibility that the calculus developed in the kidney and slipped down the dilated ureter to the level of obstruction is virtually impossible to rule out **.(13)**.

In advanced cases of ureteritis calcinosa, which is a complication of schistosomiasis ureteritis, calcification foci may develop in cysts that are exposed to the crystalloids in the urine. This could be considered as a true example of primary ureteral calculi**.(13)**.

2- Secondary ureteral calculi

Secondary ureteric stones represent the majority of ureteral calculi. They originate in the kidney and reach the ureter afterwards**.(13)**.

B- ***Composition of ureteral calculi:***

1- **Calcium oxalate:** (called a Randall's plaque), erodes through the urothelium and is a nidus for CaOx deposition. Risk factors for stone formation include dehydration, hypercalciuria, hyperoxaluria, hypernatrituria, hyperuricosuria. Urinary citrate is an important inhibitor of CaOx deposition.

2- Uric Acid Stones: risk factors for stone formation are persistently acidic urine, persistent metabolic acidosis (eg renal tubular acidosis), hyperuricosuria due to a variety of causes – Lymphoma/ leukemia treated with chemotherapy – Hyperuricemia (gout)

3- Struvite Stones: also called magnesium ammonium phosphate stone which is caused by UTIs with urease-producing organisms commonly Proteus. It can form staghorn calculi which occupy the calyceal spaces.

4- Cystine Stones: Amino acid of cysteine S-S-cysteine one of the 4 dibasic amino acids including ornithine, lysine, and arginine (COLA). Cystine stones produced in patients homozygous for recessive cystine transport gene. It is formed in acidic urine **(14).**

TREATMENT OF URETERIC STONES

1- Conservative stone treatment

1) Observation (Watchful waiting):

Conservative management of asymptomatic ureteral calculi has always been appropriate first treatment , Spontaneous stone expulsion depend on stone size . The stones less than 5 mm in the distal ureter passed spontaneously 71% to 98%. While stones larger than 5 mm fared worse with rates of 25% to 53% for distal **(15)**.

2- Traditional herbal medicine

I. Terpenes mixture (Rowatinex)

Rowatinex is used as a supportive drug in conservative stone management and stone expulsive therapy, it improves stone-free rates and reduces symptoms during stone passage **(16)**.

II. Halfa-bar (halphabarol)

This herb is recommended for medical purposes as an effective diuretic, renal or abdominal antispasmodic agent **(17)**.

3- Corticosteroids

Edema is an important factor in arresting ureteral stonepassage. Edema at the level of the stone may explain why evensmall stones cause obstruction. Antiedema agents such as corticosteroids are commonly used in conjunction with calcium channel blockers or α-blockers to treat patients with ureteral stones. Corticosteroids have good antiedema activity, are well tolerated, and cause limited side effects when given for short periods **(18)**.

5) Medical Expulsive Therapy (MET)

Rational:A stone is more likely to pass when It is located more distal in the ureter,Small in size, 68% of stones < 5mm in width will pass (usually within 40 days of symptoms onset) **(18).**

Indication: adequate renal function , Sufficient pain control, adequate oral intake

Absence of infection and Stone size < 10 mm

Contraindication: Persistent pain , Persistent vomiting, Presence of Infection or Rising Creatinine

Success rate: A 2006 meta-analysis revealed that patients with MET had a 65 percent higher probability of stone passage than those without such treatment 79

a- Calcium channel blockers

It is demonstrated that verapamil and nifedipine suppressed fastphasic contraction without affecting slow tonic contraction, suggesting that spasm may be inhibited without affectingperistaltic contraction **(Hertle and Nawrath, 1984)**.

The original MET study of patients with ureteral calculiwas a double-blind, prospective series comparing oral nifedipine with methylprednisolone versus methylprednisolone plus placebo, reporting a statistically significant difference in expulsion rates (87% versus 65%, P<0.02). **Porpiglia et al.** repeated this study as a double-blind, prospective cohort of stones in the distal ureter. A statistical difference was seen with higher expulsion rates, shorter times to expulsion and decreased analgesic use in the nifedipine and steroid group. The expulsion rate was higher for the nifedipine group versus control (79% versus 35%, P<0.05) **(19)**.

b- Alpha-1 adrenergic antagonists

They are commonly used as first-line treatment of lower urinary tractsymptoms (LUTS). The studies have reportedexcellent results with the medical expulsion therapy for thedistal ureteral calculi, with alpha-1 blockers. Their use in thetreatment of distal ureteral stones arose from the concept that they could induce a selective relaxation of the ureteral smooth muscle, which could inhibit the ureteral spasms and result indilatation of the ureteral lumen **(20)**.

Stimulation of α-1 adrenergic receptors leads to increasesin both the frequency of ureteric peristalsis and the force ofureteric contractions. However, blockage of these receptorsdecreases basal ureteric tone, peristaltic frequency and ureteralcontraction, leading to a decrease in intra-luminal pressure ofthe ureter while the rate of urine transport increases, and thusincreasing the chance of stone passage **(21)**.

Silodosin, a selective α-1A blocker, has been studied as amedical expulsive therapy. Tamsulosin preferentially blocks α-1A and α-1D adrenoceptors, with a 10-fold greater affinity thanfor α-1B adrenoceptors. In contrast, silodosin is highly selectivefor α-1A adrenoceptors, with a 162-fold greater affinity than α-1B adrenoceptors and about a 50-fold greater affinity than forα-1D adrenoceptors. Based on some studies, tamsulosin andsilodosin are equally effective as MET for

distal ureteric stones.They appear to have similar profiles in terms of expulsion ratesand times, mean number of pain episodes and need foranalgesics **(22)**.

c- Phosphodiesterase-5 inhibitors

second messengers, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), are mediators of smooth muscle relaxation. The cAMP and cGMP breakdown occurs via the activity of a family of isoenzymes known as phosphodiesterases. Phosphodiesterase (PDE) inhibitors are a class of drugs that inhibit the breakdown of cAMP and cGMP, enhancing smooth muscle relaxation **(23)**.

Phosphodiesterase-5 (PDE5) inhibitors were shown toact by a nitric oxide (NO)/cyclic guanosine monophosphate(cGMP)-signaling pathway of smooth muscles reducing the degradation of cGMP, resulting in increased levels of cGMP.Increased intracellular cGMP inhibits calcium entry into thecell, thereby decreasing intracellular calcium concentrationsand causing smooth muscle relaxation. They cause relaxation ofpenile smooth muscle leading to increased blood flow intocoropus cavernosum which allows erectile function to occur so these drugs are used in the treatment of erectile dysfunction(ED). Recently, PDE5 inhibitors have shown to cause relaxation of the ureteral smooth muscles which facilitates stone passage andexpulsion **(24)**.

Four PDE5 inhibitors (sildenafil, tadalafil, vardenafil and avanafil) are currently approved and available **(25)**. Tadalafil has been studied by some authors

In **2015,Kumar et al.** compared the efficacy of 3 drugs, tamsulosin, silodosin, and tadalafil, as MET for lower ureteralstones in a randomized study with 285 patients. The stoneexpulsion rate was 64.4%, 83.3%, and 66.7%, respectively, butthere was no significant difference between the tamsulosin andtadalafil groups (P=0.875) **(26)**.

According to the European Association of Urology (EAU) Guidelines in March 2018, patients treated with α-blockers, Ca channel inhibitors (nifedipine) and phosphodiesterase type 5 (PDE5) inhibitors (Tadalafil) are more likely to pass stones with fewer colic episodes than those not receiving such therapy. Based on studies, there is no recommendation for the use of PDE5 inhibitors in combination with α-blockers as a standard accelerating adjunct in MET **(24)**.

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