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A REVIEW ON URINARY CALCULI-TYPES, CAUSES, ITS MECHANISM, DIAGNOSIS, PREVENTION AND MEDICAL EXPULSION THERAPY OF CALCULI

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ABSTRACT

Urolithiasis is a major problem present in worldwide. The process of formation of stones in the kidney, bladder, or in urethra is called as Urolithiasis. This has been seen in all cultural and racial groups. The pathogenetic mechanisms of stone formation are complex and they involve both metabolic and environmental risk factors. Stone formation is one of the painful urologic disorders that occur in about 12% of the global population and its re-occurrence rate in males is about 70-81% whereas 47-60% in female. Over the past 20 years, kidney stones become worldwide problem with a marked increase in prevalence. The hallmark of stones that obstruct the ureter or renal pelvis was extreme intermittent pain that radiates from the flank to the groin or to the genital area and inner thigh. The stone type is usually named after its mineral composition. The most common type of kidney stones found in worldwide contains calcium. The modality of treatment depends on many factors like size of stone, type of stone and site of stone. Medical treatments for expulsion of urinary calculi provide a noninvasive, relatively cheaper and safer alternatives to open surgery as well as to minimally invasive surgery for

small stones. Medical expulsive therapies, especially alpha-blockers and calcium channel blockers have been shown to be effective in expulsion of urinary calculi.

KEYWORDS: Urolithiasis, Kidney stone, Medical expulsive treatment.

INTRODUCTION

Urolithiasis is a very common problem present worldwide. The process of formation of stones in the kidney, bladder, or in urethra is called as Urolithiasis.[1] Stone formation is a painful disorder that plays a major role in daily urologic practice. Stone formation disorders occurs in about 12% of the global population and its re-occurrence rate in males is about 70-81% and 47-60% in females.[1] Over the past 20 years, kidney stones become worldwide problem with a marked increase in prevalence. The hallmark of stones that obstruct the ureter or renal pelvis was extreme intermittent pain that radiates from the flank to the groin or to the genital area and inner thigh.[1] Some countries have high incidence of calculi mainly due to climate, diet habits, local geology with hydro mineralogy and sanitation. Rising global temperatures also lead to an increase in kidney stones, which is reported at the 103rd Annual Scientific Meeting of the American Urological Association. Dehydration also link to stone disease, particularly warmer climates will exacerbate this effect.[2] Lifestyle changes in diet pattern and global warming also influence these effects.[3] The rate of occurrence of stone is three times higher in men compared to the women, because of the enhancing capacity of testosterone and the inhibiting capacity of estrogen in stone formation. The stone type are mainly named after its mineral composition.[1] The most common type of kidney stones found in worldwide contains calcium. MET (Medical Expulsive Therapy) has become a standard protocol for treatment of small stones in the urinary system. It increases the rate of expulsion and reduces the expulsion time. Up to 4mm size are expelled easily in almost all cases with MET. Spontaneous expulsion rate for 4-6mm stones is about 25% and over 8mm size are rarely expelled with MET.[3] Different procedures have been recommended for stone removal of greater than 5mm size like Ureteroscopy (URS), Extracorporeal Shock Wave Lithotripsy (ESWL), Percutaneous Nephrolithotomy (PCNL), and open/laparoscopic stone removal. The information on the location, size, and shape of the stone is essential for proper selection of treatment procedure.[4] The time required for the stone expulsion depends on the size of the stone. Smaller the stone, faster its expulsion and clearance. Extra corporeal shock wave lithotripsy [ESWL] is the first line for the management for ureteric stones of less than 20mm size. Success rate with ESWL in stones of over 8mm size in distal ureter is from 49.9% to

91.1% and the rate decreases as the stones size increases. While few centers use Ureteroscopy [URS] as their first line treatment to achieve better stone free rate.[3] MET is very easy and a cheap procedure, can be preferred as first line treatment before ESWL or URS.

TYPES OF STONES FOUND IN URINARY SYSTEM

1. Calcium stones

The most common type of kidney stones found in worldwide contains calcium. Calcium stones are mainly formed by calcium oxalate, or combination with calcium phosphate or calcium urate. Predisposing factors for the cause of these type stones are; low urine volume, hypocitraturia, hyperoxaluria, hypercalciuria, hyperparathyroidism, malignancy, renal tubular acidosis, sarcoidosis and excess vitamin. Microscopically calcium oxalate stones appear as 'envelopes'.[1,2]

2. Uric acid stones

A diet rich in animal protein and high purine content may lead to increase the risk of uric acid stone formation. People with certain metabolic abnormalities such as obesity may also produce uric acid stones. Other conditions likely to cause uric acid stone formation are hyperuricosuria with or without hyperuricemia, disorders of acid/base metabolism. The diagnosis of uric acid urolithiasis is analyzed by the presence of a radiolucent stone in the face of persistent urine acidity, in conjunction with the finding of uric acid crystals in fresh urine samples. Uric acid stones will appear as pleomorphic crystals, usually diamond-shaped. Uric acid stones also look like squares or rods which are polarizable. Patients with hyperuricosuria can be treated with allopurinol which reduce urate formation. Urine alkalization may also be helpful in this situation.[1,2]

3. Cystine stones

Cystine stones occurs mainly due to cystinuria, an inherited disorder of the transport of an amino acid called Cystine, which results in excess amount of cystine in the urine (Cystinuria) and thus leads to formation of cystine stones. Cystinuria affects equally for both genders. Cystine then tends to precipitate out of urine and form stones (Calculi) in the urinary tract. Small stones will pass through urine, while big stones remain in the kidney (nephrolithiasis) impair the outflow of urine and medium-size stones move from the kidney into the ureter and lodge there, which blocks the flow of urine. The obstruction of the urinary tract puts pressure on both ureter and kidney causing the ureter to dilate and the kidney to be compressed. Obstruction also causes the urine to be stagnant which an open invitation for repeated urinary

tract infection. The pressure on the kidneys and the urinary infections leads to damage to the kidneys. The damage can further progress to renal insufficiency and end-stage kidney disease, requiring renal dialysis or a transplant. Signs and symptoms of cystinuria, includes:

- Hematuria - Blood in the urine
- Flank pain –Pain occur in side, due to kidney pain
- Renal colic - Intense, cramping pain due to stones present in the urinary tract
- Urinary tract Infections[1,2]

4. Silicate stones or drug induced stones

Very rarely occurring one. Stones can formed as a result of taking certain medications or herbal products and the subsequent build-up of chemicals from those products in the urine may lead to stone formation .Some of them are Loop diuretics, Acetazolamide, Topiramate, Zonisamide, Laxatives, Ciprofloxacin, Sulfa medications, Triamterene, Indinavir, Ephedrine, Guaifenesin and products containing silica.[1]

5. Struvite stones

Struvite stones were also known as infection stones or triple phosphate stones. Urease-producing bacteria, most commonly; Proteus and Klebsiella are responsible for this infection stones. Struvite stone formation mainly occurs when there is increased ammonia production and elevated urine pH which decrease the solubility of phosphate. These infection stones are commonly seen in people who have predisposing factors to cause urinary tract infections, such as those with spinal cord injury and other forms of abnormalities like neurogenic bladder, ileal conduit urinary diversion, vesicoureteral reflux, and obstructive uropathies. Also they are commonly seen in people with underlying metabolic disorders, such as idiopathic hypercalciuria, hyperparathyroidism and gout. This infection stones can grow rapidly, forming large calyceal staghorn (antler-shaped) calculi which require invasive surgery such as percutaneous nephrolithotomy for definitive treatment.[1,2]

CAUSES OF STONE FORMATION

Various factors plays an important role in increasing the risk of stone formation for some people. It includes;

1. Excess amount of calcium, phosphate, oxalate and uric acid in the urine

Calcium is the main component of all common type of human kidney stones. Unlike supplemental calcium, high intake of dietary calcium was not appear to cause kidney stones and it actually protect against their development this is because of the role of calcium in

binding the ingested oxalate in the gastrointestinal tract. If the amount of calcium intake decreases, the amount of oxalate available for absorption into the bloodstream increases, this oxalate then excreted in greater amount through urine by the kidneys. In the urine, oxalate is a very strong promoter for calcium oxalate precipitation. Besides the Calcium other electrolytes that influence the formation of kidney stones includes, high dietary sodium, fluoridation of drinking water.

Besides all these, high dietary intake of potassium appears to reduce the risk of stone formation because potassium promotes the urinary excretion of citrate, which is an inhibitor of urinary crystal formation and high dietary intake of magnesium also reduces the risk of stone formation because magnesium is also an inhibitor of urinary crystal formation.[1,2]

2. Lack of stone inhibitors in the urine

Normal urine contains chelating agents such as citrate which inhibit the nucleation, growth and aggregation of calcium-containing crystals. Other endogenous inhibitors include calgranulin, Tamm-Horsfall protein, glycosaminoglycans, uropontin, nephrocalcin, prothrombin F1 peptide, and bikunin. The biochemical mechanism of action of these substances have not yet been thoroughly elucidated. However, when these substances falls below their normal proportions, stones can form from an aggregation of crystals.[1,2]

3. Inadequate hydration

Dietary factors also increases the risk of stone formation, they include low fluid intake, high dietary intake of animal protein, sodium, refined sugars, fructose ,high fructose corn syrup, oxalate, grapefruit juice, apple juice, and cola drinks.

4. Medications

Loop diuretics, Acetazolamide, Topiramate, Zonisamide, Ciprofloxacin, Sulfa medications, Triamterene, Indinavir, Ephedrine and Guaifenesin.

5. Ongoing urine infection

Commonly stone formation occurs due to inadequate urinary drainage, foreign bodies in urinary tract, microbial infections.

6. Rare inherited conditions

7. Family history of stone formation

8. Vitamins

There was a belief in the medical community that, ingestion of vitamin C supplements is associated with an increased incidence of kidney stones and excess dietary intake of vitamin C also promote the risk of calcium oxalate stone formation. Excessive vitamin D supplementation may also increase the risk of stone formation by increasing the intestinal absorption of calcium.[1]

9. Super saturation of urine

When the urine contains one or more calculogenic (crystal-forming) substances, a crystal seed may form through the process of nucleation. This seed crystal adhere to cells on the surface of renal papilla and aggregate into an organized mass. Depends upon the chemical composition of the crystal, the stone-forming process may proceed more rapidly when the urine pH is unusually high or low. Super saturation of the urine is a pH-dependent process. Super saturation of urine can be the leading cause of uric acid stones and cystine stones. The formation of uric acid stones requires a combination of both hyperuricosuria (high urine uric acid levels) and low urine pH.[1]

10. Others

There were no conclusive data demonstrating a cause and effect relationship between alcohol consumption and kidney stones. However, some have theorized that certain behaviors associated with frequent drinking can lead to systemic dehydration, which can leads to the development of kidney stones.[1]

MECHANISM OF STONE FORMATION

The pathogenesis of kidney stone is a complex biochemical process which remains incompletely understood. Renal stone formation is a biological process that involves a physicochemical changes and super saturation of urine. Due to super saturation, solutes precipitate in urine which leads to nucleation and then crystal concretions are formed. The crystallization occurs when the concentration of two ions exceeds their saturation point in the solution. The transformation of a liquid into a solid phase is influenced by the pH and specific concentrations of excess substances. The level of urinary saturation along with the stone-forming constituents like calcium, phosphorus, uric acid, oxalate, cystine, and low urine volume are risk factors for crystallization. The sequence of events leading to stone formation includes:

- **Crystal nucleation**

The first step in the formation of kidney stone is the transformation of liquid to a solid phase in a supersaturated solution called as nucleation. In a supersaturated liquid, free atoms, ions, or molecules start forming microscopic clusters which precipitate when the bulk free energy of the cluster is less than that of the liquid. In supersaturated solutions, if promoters exceeds than inhibitors, nucleation starts. Epithelial cells, urinary casts, RBCs, and other crystals can also act as nucleating centers in urine in the process of nuclei formation, known as heterogeneous nucleation. Once a nucleus is created, crystallization will occur. The crystallization can occur at lower chemical pressure than they required for the formation of the initial nucleus. On the other hand renal tubular cell injury can promote crystallization of CaOx crystals by providing substances for their heterogeneous nucleation.[5,6]

- **Crystal growth**

Crystal growth is one of the essential step in the particle formation and also for stone formation. Crystals in urine stick together to form a small hard mass of stone, which is referred as crystal growth. In each step of stone formation, both crystal growth and aggregation have important functions. Stone growth is accomplished through aggregation of crystals or secondary nucleation of crystal on the matrix-coated surface. The process of stone is very slow and requires longer time to obstruct the renal tubules.[5,6]

- **Crystal aggregation**

The process whereby a small hard mass of a crystal in solution sticks together to form a larger particle is called aggregation. Crystal aggregation is one of the most important step in stone formation. All the models of CaOx urolithiasis concludes that, crystal aggregation is probably involved in crystal retention within the kidneys. [5,6]

- **Crystal-Cell interaction**

After the crystallization, the formed crystals will attach to the renal epithelial cells termed as crystal retention or crystal-cell interaction. The Crystal-cell interaction results in the movement of crystals from basolateral side of cells to the basement membrane. Most of the crystals attached to epithelial cells will be digested by macrophages or by lysosomes inside cells and then discharged with urine. Following by renal tubular cell injury, cellular degradation produces numerous membrane vesicles which are nucleators of calcium crystals. Khan et al. concluded that crystal-cell interaction plays an important role in the development

of urinary stone disease. Although the mechanisms of crystal-cell interaction are thought to be very complex and many of them remain unexplored. [5,6]

- **Endocytosis of CaOx Crystals via renal tubular epithelial cells**

Endocytosis or engulfment of crystals by renal tubular cells is an earliest process in the formation of kidney stones. Many substances have an inhibitory effect on CaOx crystal endocytosis. Tamm-Horsfall protein (THP) in distal tubular fluid leads to decreased COM (calcium oxalate monohydrate) crystal endocytosis by 34% by blocking the uptake of COM crystals by cells present in nephron and thus prevent renal crystal retention and stone formation. Whereas the inhibitory effect of FN (fibronectin) on CaOx crystal endocytosis was only 18.4%[5,6]

- **Cell Injury and Apoptosis**

Exposure to high levels of oxalate or CaOx crystals induces epithelial cellular injury, which is a predisposing factor to stone formation .CaOx crystal deposited will help in the synthesis of macromolecules that can promote inflammation. Crystals then may be endocytosed by cells or transported to the interstitium. It is noted that injured cells develop a nidus which promotes the retention of particles on the renal papillary surface .In individuals with severe primary hyperoxaluria, renal tubular cells are injured and crystals become attached to them. The addition of CaOx crystals onto Madin–Darby Canine Kidney (MDCK) cell lines showed an increase in the release of lysosomal enzymes, prostaglandin E2, and cytosolic enzymes. A study on animal models also revealed that the administration of high concentrations of CaOx crystals or oxalate ions appears to be toxic causing the renal tubular cell damage. It is discovered that increase in oxalate, increases the availability of free radicals by inhibiting enzymes responsible for their degradation. The reactive oxygen species can damage the mitochondrial membrane and reduce its transmembrane potential, these known events are features of early process in apoptotic pathways. The exposure of renal cells to oxalate will increases an altered gene expression that induces apoptosis signaling. Apoptosis at the level of renal tubular cells may lead to stone formation through cellular demise and post apoptotic necrosis which could promote calcium crystal aggregation and growth., However, it was noted that some cells did not respond to oxalate injury, it may be due to the fact that changes in gene expression could protect from apoptosis and then inhibit from lithiasis. [5]

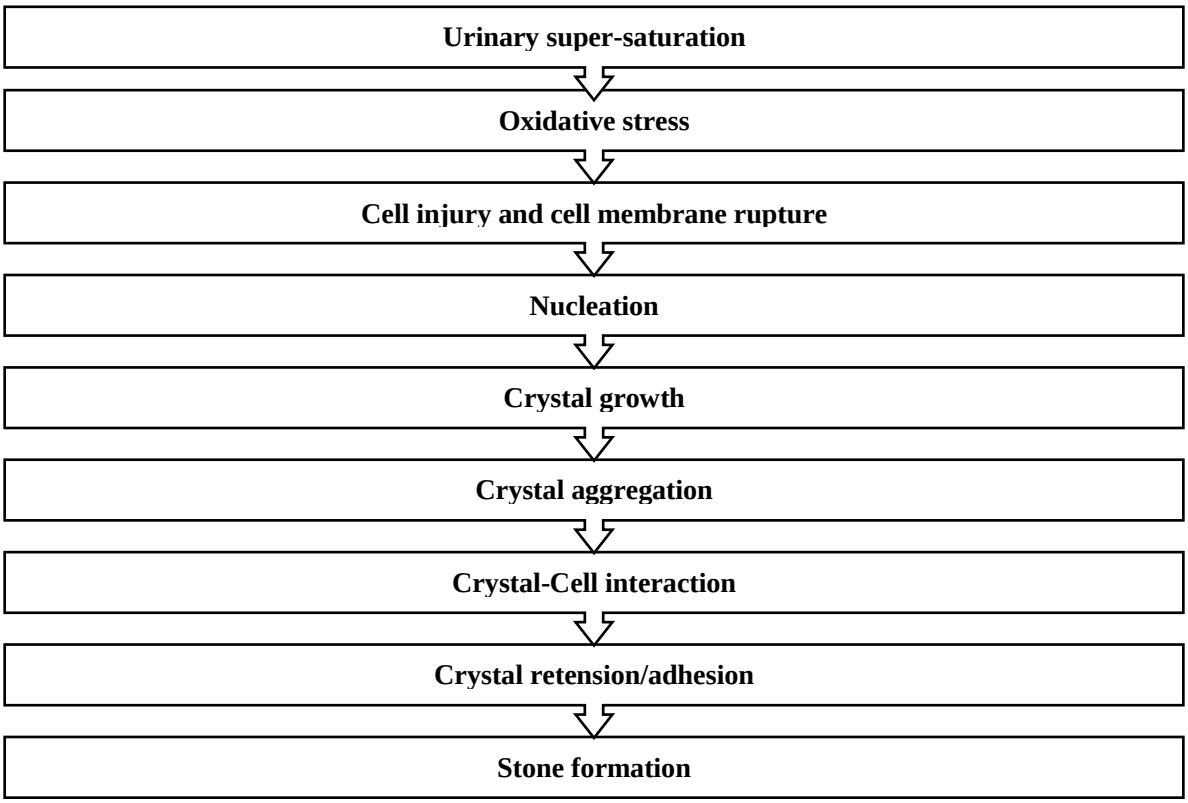
- **Randall's Plaques**

The precursor's origin of urinary stone is appeared as Randall's plaques. Moreover, the pathogenesis of Randall's plaque itself is not clearly known.Randalls plaque plays an important role in precipitate kidney stone formation in idiopathic calcium oxalate stone formers. The majority of CaOx stones are found to be attached with renal papillae at the sites of Randall's plaques. It is located at the interstitial basement membrane in the loop of Henle. Calcium phosphate and purine crystal compositions were identified in plaques, Initially, these plaques deposit in the basement membranes of the thin loops of Henle and extend further into the interstitial space to the urothelium, The regions of plaques will expose to urine after the urothelium, loss their intergrity. The exposed surface will then covered by molecules like osteopontin, TammHorsfall protein and the crystals formed from urine saturation result in formation of ribbon of alternating matrix and crystal layer, by repeated coating and crystallization. These crystallization will escape from matrix modulation and the crystals extend outward the space of urine and result in formation of calcium oxalate stone.[5]

- **Kidney stone Inhibitors and Promoters**

Inhibitors are those substances which decrease the formation of super saturation, nucleation, crystal growth, rate of aggregation, or any other processes that required for the stone formation. Normally, the urine itself contains chemicals that prevent crystal formation. Inhibitors present in urine includes small organic anions such as citrate, small inorganic anions such as pyrophosphates, multivalent metallic cations such as magnesium, or macromolecules like osteopontin, glycosaminoglycans, glycoproteins, urinary prothrombin fragment-1, and Tamm–Horsfall proteins. These inhibitors do not seem to work equally for every individual, therefore in some people it leads to stones formation. But, if the formed crystals are tiny, it will travels through the urinary tract and passes out from the body with urine splash without being noticed. In contrast, promoters are substances which facilitate stone formation by different mechanisms. Some of the promoters include cell membrane lipids, calcitriol hormone enhancement via parathyroid hormone stimulation, oxalate, calcium, sodium, cystine, and low urine volume. In general, the imbalance between both urinary stone inhibitors and promoters has been suggested to be the cause for stone formation. [5]

Schematic representation of the various events of kidney stone formation are shown in below figure;



DIAGNOSIS OF URINARY CALCULI

To identify the risk factors for urinary stones usually a 24hr urine sample is collected and measure the following;

- Serum electrolytes: calcium, phosphate, bicarbonate,uric acid
- Urinalysis, including urine pH and urine culture
- Blood urea nitrogen, serum creatinine
- Parathyroid hormone, if elevated serum calcium
- Stone analysis, if possible
- Measure cystine in urine.
- Radiological investigations:

❖ Computed Tomography(CT scan) is one of the best imaging method to confirm (99% diagnostic accuracy) the diagnosis of a urinary stone in a patient with acute flank pain.It also helps to measure the stone density and may guide in its treatment

❖ Plain abdominal film (kidney-ureter-bladder(KUB) view) is important to assess the radio-opacity of stone and to monitor stone progression[7]

CLINICAL FEATURES OF URINARY TRACT STONES

Urinary tract symptoms

- Pain—Loin to groin pain,colicky pain
- Haematuria
- Dysuria and strangury

Systemic symptoms

- Restless patient, often writhing in distress
- Nausea, vomiting, or both
- Fever and chills (If associated infection)

Asymptomatic

- Incidental stones(One third may be seen as symptomatic) [7]

PREVENTION OF STONE FORMATION[7]

- Increase the water intake in order to maintain a urine output of at least 2 liter per day :
  It is the simple and most important lifestyle change to prevent stone because fluid intake reduce urinary saturation and dilutes promoters of CaOx crystallization.
- Decrease intake of animal protein:
  Animal proteins may raise the acid load because of its high content of sulfur-containing amino acids.
- For prevention of calcium oxalate, cystine, and uric acid stones, urine should be alkalinized by eating a diet rich in fruits and vegetables,by intaking supplemental or prescription citrate, or drinking alkaline mineral waters.
- Cranberry juice:
  Decreases the oxalate and phosphate excretion and increases the citrate excretion
- Increase citrus friuts intake
- Decrease dietary oxalate:
  Reduce intake of foods rich in oxalate-spinach, rhubarb, chocolate, and nuts
- Restrict salt intake (≤ 50 mmol/day of sodium chloride)

MEDICAL MANAGEMENT FOR EXPULSION OF URINARY CALCULI

- **Alpha blockers**

Current best medical practice guidelines recommend alpha-blockers for the expulsion of distal ureteral stones. Alpha –blockers or alpha-1 antagonists, act by preventing stimulation

of smooth muscle which regulate the diameter of smaller veins and arteries and the urinary system through inhibiting adrenergic agonist like norepinephrine. The incresed diameter of urinary system help to easy passage of stone. Patients treated with alpha-blockers had a 65% greater likelihood of spontaneous stone passage. The 2016 European Association of Urology guidelines for management of urolithiasis recommended the use of alpha- blockers along with NSAIDs in expulsion of calculi. Tamsulosin has been the most studied alpha-blocker in MET. A randomized control trial by Yilmaz and colleagues demonstrated that Tamsulosin, Terazosin, and Doxazosin were equally effective in distal stone expulsion in comparison to the control group. [8,9]

- **Calcium channel blockers**

Nifedipine is the only calcium channel blocker that shows some benefit in stone expulsion. Studies indicated that nifedipine can be effective in reducing renal colic, but the improvement in stone expulsion rate was minimal. Alpha-blockers are significantly better than nifedipine in facilitating stone passage and relieving renal colic. Due to this, recent EAU guidelines do not recommend calcium channel blockers as a monotherapy for MET. But it can be safely used in conjunction with alpha-blockers in patient population as their side effects have been found as insignificant. [8,9]

- **Corticosteroids**

Urinary calculi will cause ureteral inflammatory reactions and submucosal edema around the stone region, which may aggravate urinary obstruction and retention of calculus. Corticosteroids help to decrease inflammation and edema related irritation. Corticosteroids are administered for short duration because of its adverse efffet on prologed usage. However in patients with diabetes, gastric ulcers, or steroid intolerance, corticosteroid therapy should be avoided. [8,9]

- **Phosphodiesterase -5 inhibitors**

A novel topic in MET is the use of PDE-5 inhibitors in stone expulsion. PDE-5 inhibitors mainly act by a nitric oxide/cyclic guanosine monophosphate (cGMP)-signaling pathway which result in increased levels of cGMP, which further leads to smooth muscle relaxation in the ureter. Drugs under PDE-5 inhibitors are; Vardenafil, Sildenafil, and Tadalafil. However further studies are required to assess the utility of PDE5 inhibitors in MET. [9]

CONCLUSION

The present review explains about the cause, types, mechanism, diagosis, prevention and medical expulsion therapy for urinary calculi. It concludes that the most common type of kidney stones found in worldwide contains calcium. The pathogenesis for formation of renal stone is a biological process that involves both physicochemical changes and super saturation of urine. Medical therapies for primary expulsion of renal and ureteric stones, especially with the use of alpha-blockers and calcium channel blockers have shown to be effective.

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