

## Medical Therapy to Facilitate Urinary Stone Passage

MUHAMMAD NASIR JAMIL<sup>1</sup>, MUHAMMAD SHAHZAD<sup>2</sup>, HAMZA ASHRAF<sup>3</sup>, EHSAN UL ISLAM<sup>4</sup>

<sup>1,2</sup>Associate Professor Urology, Ayub Medical Teaching Institution Abbottabad, Pakistan.

<sup>3</sup>Assistant professor Urology, Women Medical College Abbottabad, Pakistan.

<sup>4</sup>PGR Urology, Ayub Teaching Hospital, Medical Teaching Institute, Abbottabad, Pakistan.

Correspondence to Dr. Muhammad Nasir Jamil, Email: [tamimrai18@gmail.com](mailto:tamimrai18@gmail.com)

### ABSTRACT

**Background:** Urinary stones are now a worldwide problem due to a rise in occurrence over the past few decades. All racial and cultural groups have experienced this. Complex metabolic and environmental risk factors are both involved in the pathogenetic pathways of stone production. This disease affects roughly 12% of the world's population. Its recurrence rate is about 70% in men and 47% in women. Urinary stones have significantly increased in prevalence over the past 20 years, becoming a global disease.

**Aim:** This review covers literature on the medical therapy of urolithiasis to facilitate urinary stone passage and their mechanism of action in the light of the new data on the diagnosis and different types of urinary tract stones.

**Method:** A preliminary search of related articles was obtained from three online databases PubMed, Sci.hub and Google scholar which were used to conduct a systematic evaluation of the literature. Inclusion and exclusion criteria screened the initial search results, and 67 papers were chosen to be appropriate for this literature review following careful reading, analysis, and evaluation.

**Results:** Different methods of medical therapy (phosphodiesterase-5 inhibitors, alpha blockers, calcium blockers, non-steroidal anti-inflammatory drugs and different types of surgical procedures (extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, ureteroscopy) were thoroughly reviewed but among all of them the expulsion rate to remove the urinary stone was found to be larger and faster in calcium channel blocker (CI 1.33-1.66) and alpha blockers (CI 1.152-7.45).

**Practical implications:** Medical therapies facilitate the urinary-stone passage but these therapies are not generally used. The choices for treating urinary stones are expanded by these techniques. Patients with big ureteral stones have had better results with medical expulsive therapy. Removing the urinary stones also decreases the chances of other diseases which happened as a result of urinary stone. There are many benefits of medical expulsive therapy which are diverse in nature and this therapy minimizes the exposure to anesthesia and radiations.

**Conclusion:** Different surgical procedures are used to remove the stones from the urinary passage. Despite of surgical procedures, medical expulsive therapy are more helpful. Alpha-blockers and calcium channel blockers are the main medical expulsive therapies for primary evacuation of urinary tract stones.

**Keywords:** Urolithiasis, Urinary tract stones, Medical expulsive treatment.

### INTRODUCTION

Urolithiasis is a widespread disease that exists everywhere. Urolithiasis is the medical term for the development of kidney, bladder, or urethral stones<sup>1</sup>. A significant portion of daily urologic practice involves the painful disease known as stone development. Over 12% of the world's population has a disorder of stone production, and the recurrence rate is roughly 70-81% for men and 47-60% for women<sup>2</sup>. Kidney stones have significantly increased during the past 20 years, becoming a concern on a global scale. Extreme intermittent pain radiating from the genital region and inner thigh is the defining feature of stones that clog the ureter or renal pelvis.

In Europe and the USA, the lifetime chance of getting urolithiasis is reportedly between 5 and 12%. 7% of women and 13% of males suffer from this disorder<sup>3,4</sup>. In 2000, the United States had nearly 2 million outpatient visits related to urolithiasis, with total inpatient and outpatient costs amounting to \$2.1 billion<sup>4,5</sup>. Approximately 70% of people with urolithiasis are between the ages of 20 and 50 and the recurrence rate is close to 50% over a 10-year period<sup>4,6,7,8,9,10</sup>. In 1994, urolithiasis was 5.2% and by 2017, that percentage has more than doubled. This rise in prevalence is linked to more than a million emergency department visits and more than 40,000 surgical procedures per year. Costs are approaching \$5 billion year, and they will probably continue to rise<sup>11,12,13,14</sup>. The morbidity associated with renal colic, which can cause abrupt, excruciating pain, is one of the main problems with urolithiasis. Sepsis and death from a blocked, diseased stone are examples of severe consequences. Though mortality rates have decreased, recent prospective data indicate an increase in the incidence of infected urolithiasis and rates of sepsis and severe sepsis<sup>15</sup>. The main causes of high calculi occurrence in some nations are the local geology, nutrition, hydro mineralogy, and

sanitation. According to research presented at the American Urological Association's Annual Scientific Conference, increase in temperature also contribute to an increase in kidney stones. Stone disease and dehydration are linked, and warmer climates will increase this effect<sup>16</sup>. Global warming, lifestyle modifications, and dietary patterns all affect the passage of urinary tract.

For the removal of stones larger than 5 mm, a number of procedures have been suggested, including ureteroscopy, extracorporeal shock wave lithotripsy, percutaneous nephrolithotomy, and open/laparoscopic stone removal. Understanding the placement, size, and shape of the stone is crucial to choose the most appropriate course of treatment<sup>17</sup>. Depending on the size of the stone, evacuation takes a certain length of time. With increased expulsion and removal speed, the size of the stone shrinks. The principal form of therapy for ureteric stones smaller than 20 mm is extracorporeal shock wave lithotripsy (ESWL). With distal ureter stones larger than 8 mm, the success rate with ESWL ranges from 49.9% to 91.1%, and the proportion decreases as the stone size increases. However, fewer clinics use ureteroscopy (URS) as their initial course of treatment to raise the proportion of patients who do not have stones<sup>18</sup>. The term "medical expulsive therapy" (MET) refers to the use of drugs to reduce peristaltic activity and relax the smooth muscles of the ureter. The use of medications to aid ureteral stone passage prior to surgery is referred to as "medical expulsive therapy" (MET). Calcium channel blockers and alpha-blockers are the two medication classes that are most frequently utilised in medical expulsive therapy<sup>19,20</sup>. Tamsulosin was investigated largely in patients with bladder dysfunction brought on by spinal dysraphism, and paediatric exclusivity for the drug which was granted by the FDA in 2009. This stance on tamsulosin was upheld by the FDA's Pediatric Advisory Committee in 2012, and it has continued for regular monitoring procedures for negative effects<sup>21</sup>.

Tamsulosin was found to be beneficial for treating adult MET in a meta-analysis in 2019 that included 2763 participants from 29 randomised control trials (RCTs). After adjusting for stone size and

Received on 25-10-2022

Accepted on 15-03-2023

location, Tasian et al. (2014) reported that tamsulosin medication increased spontaneous transit of ureteral calculi with an odds ratio (OR) of 3.31 (95% confidence interval (CI) in a multi-institutional retrospective cohort of 334 eligible children (1.49-7.34)<sup>21</sup>. In a prior meta-analysis, Velázquez et al. (2015) found that children using MET had a higher success rate of passing ureteral stones<sup>22</sup>. The number of prospective RCTs reported was low (n=3), and that meta-analysis data from two retrospective cohorts. Similar results favoring MET for spontaneous passing were found by Tian et al. in a related meta-analysis that synthesized 4 RCTs and 1 retrospective cohort in 2017<sup>23</sup>.

**TYPES OF STONE:** Although there are many distinct kinds of stones, 80% of them are made of calcium oxalate or phosphate. Other less common stone kinds include those formed of struvite (10%), cystine (1%), and uric acid (9%)<sup>2</sup>. Food, a personal or family history of stones, environmental variables, medications, and the patient's medical history are some of the risk factors for the many types of stones. Kidney stones are known to occur when oral hydration is insufficient, a high protein diet from animal sources, a high oxalate intake from foods including beans, beer, berries, coffee, chocolate, some nuts, some teas, soda, spinach, and potatoes, as well as a high salt intake<sup>24</sup>.

**Calcium stones:** The most common type of kidney stone found worldwide contains calcium. The main contributor to calcium stones is calcium oxalate, either on its own or in combination with calcium phosphate or calcium urate. Predisposing variables for the development of different types of stones include low urine volume, hypocitraturia, hyperoxaluria, hypercalciuria, hyperparathyroidism, malignancy, renal tubular acidosis, sarcoidosis, and high vitamin intake. Under a microscope, calcium oxalate stones appear to be envelopes<sup>24</sup>.

**Uric acid stones:** Low urinary uric acid levels, low urine pH, and low urinary volume are all associated with the development of uric acid stones. Nonetheless, these patients frequently report as idiopathic uric acid stone formers despite the fact that metabolic diseases including diabetes and obesity would also increase the likelihood of uric acid stones. Under a pH of 5.5, low urine pH will normally encourage the formation and deposition of uric acid crystals. Animal protein-rich diets will increase the load and precipitation of uric acid. Also linked to the development of uric acid stones are gout, a number of neoplastic diseases, and persistent diarrhoea<sup>25,26</sup>.

**Struvite stones:** Struvite stones, often known as infection stones, are less prevalent and may manifest gradually before symptoms appear. The renal collecting system could become overburdened by a stone of this type if it were to develop into a large calculus or staghorn. They are composed of magnesium ammonium phosphate and develop as a result of elevated urine pH, which is primarily caused by the presence of urease produced by *Proteus* or *Klebsiella* species. The breakdown of urea produces ammonia, which elevates the pH of the urine (often to more than 8), which encourages the formation of struvite stones<sup>(27)</sup>.

**Cystine stones:** The rare condition of cysteine stones is caused by mutations in the SLC3A1 and SLC7A9 genes. The prenatal condition that caused these mutations is inherited. Poor cystine metabolism and transport brought on by these mutations result in cystinuria and stones. They frequently appear throughout childhood or adolescence, but they can also occur in newborns. Furthermore, staghorn calculi may develop from cystine stones..

**Drug induced stones:** Drug-induced urolithiasis only accounts for 2% of stone formation, which is extremely rare. Two protease inhibitors that are commonly used to treat HIV are sulfadiazine and atazanavir. Due to their difficulty in being seen on enhanced CT scans and the presence of gelatinous substance, protease inhibitor stones commonly resist lithotripsy. A significant urinary obstruction necessitating ureteral stenting is typically the result<sup>28,29</sup>. It has been proven that patients receiving long-term medication have a higher risk of getting stones when taking ceftriaxone<sup>30</sup>.

Table 1: Different types of stones and their medical abnormality<sup>30</sup>.

Stone types	Medical abnormality
Calcium	Hyperoxaluria, Hypercalciuria, Hypocitraturia
Uric acid	pH of urine below 5.5 Hyperuricosuria
Struvite	High urethral ammonia As well as bicarbonate levels
Cystine stones	Cystinuria
Drug induced stones	Triamterene, Guaifenesin

**FIXING FACTORS FOR STONE FORMATION:** Some persons have a higher risk of developing stones due to a number of circumstances. It includes:

**Urine with excessive levels of phosphate, calcium, oxalate, and uric acid:** Every type of typical human kidney stone contains calcium as its main component. Increased dietary calcium intake does not appear to promote the development of kidney stones and may even be protective against it because calcium is involved in so many processes. Binding the oxalate that has been ingested in the digestive tract. Oxalate is more readily available for bloodstream absorption when calcium intake is reduced, and the kidneys eliminate more oxalate through urine as a result. Oxalate is a particularly potent activator of calcium oxalate precipitation in the urine. Together with calcium, excessive dietary salt and water fluoridation are other electrolytes that can affect kidney stone formation<sup>16,17,32</sup>.

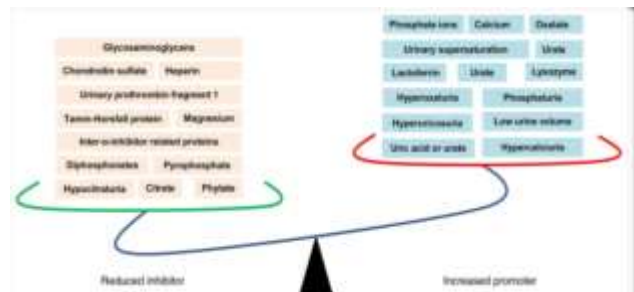
**Lack of stone inhibitors in the urine:** Chelating substances like citrate, which are present in typical urine, prevent the formation, development, and aggregation of calcium-containing crystals. Calgranulin, the Tamm-Horsfall protein, glycosaminoglycans, uropontin, nephrocalcin, prothrombin F1 peptide, and bikunin are some of the additional endogenous inhibitors. These drugs' molecular mechanisms of action have not yet been fully understood. Yet, a crystallised aggregate of these chemicals can form stones when their regular ratios are not maintained<sup>25</sup>.

**Medications:** Different kinds of medicines are also the causes of stone formation in the urinary passage like Loop diuretics, Ciprofloxacin, Acetazolamide, Sulfa medications, Guaifenesin, Triamterene, Indinavir and Ephedrine<sup>32</sup>.

**Ongoing infection in the urine:** Frequent causes of stone formation include poor urine drainage, urinary tract foreign materials, and microbial infections.

**Vitamins:** It was once believed in the medical community that consuming too much vitamin C through food increased the risk of calcium oxalate stone production and that taking vitamin C supplements increased the risk of kidney stones. Excessive vitamin D intake may increase the risk of stone formation by increasing the intestinal absorption of calcium<sup>16,17,32</sup>.

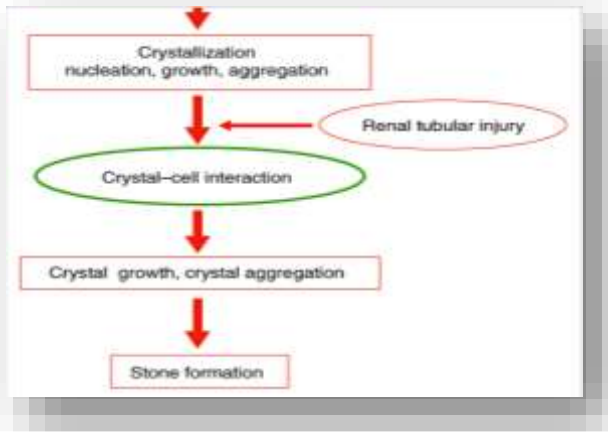
Figure 1: Different types of inhibitors and promoters are suggested to play important role in the formation of stones<sup>31</sup>



**MECHANISM OF STONE FORMATION:** Renal calculi are formed when the high volume of crystals that make up the stone begin to build up and crystallise within the parenchyma of the kidney as a result of urolithiasis, which is caused by the supersaturation of the urine by the stone's high concentration of crystals. These crystals will coalesce, keep expanding, and may even enter the ureter, where they may produce symptoms. If the stone plugs the ureter

and restricts urine flow through it, hydronephrosis can form as a result of upstream ureter and renal pelvis dilatation. The ureteropelvic junction (UPJ), where ureteral blockages from stones most frequently occur, is a result of the ureter's narrow diameter in this region. The ureter passes the iliac vessels and the ureterovesical junction, which are the other two locations where the ureter narrows (UVJ). Increased luminal tension and hydronephrosis will result in prostaglandin release, which will induce the colicky pain associated with the syndrome as stones pass through the ureter<sup>32,35,36</sup>.

Figure 2: Schematic diagram of formation of stone<sup>37</sup>



**MEDICAL EXPULSIVE THERAPY:** Medical expulsive therapy (MET) is a workable, conservative treatment option for the management of distal ureteral stones. Inhibitors of phosphodiesterase-5 (PDE5), calcium channel blockers, corticosteroids, and alpha-blockers are a few examples of medications that have been mentioned as medical treatment options. The possibility of a stone passing through the ureter is influenced by the size of the stone and the condition of the ureter. The reported spontaneous passing rates for distal ureteral stones between 5 and 10 mm range from 25% to 53% and from 71% to 98% for stones less than 5 mm<sup>38,39,40,41</sup>.

**Alpha blockers:** Alpha-blockers' function in MET has been extensively discussed. Alpha-blockers are advised by current best practice standards for the ejection of distal ureteral stones. The American Urological Association (AUA) and the European Urological Association (EAU) both describe the use of alpha-blockers as a potential treatment for certain patients who are familiar with the method and in situations when rapid surgical stone removal is not necessary<sup>41,41,43</sup>. The basis for their usage was studies in animal models that showed how alpha-blockers affect ureteral stones by increasing the amplitude of ureteral smooth-muscle contraction, decreasing the frequency of peristaltic contractions, and decreasing ureteral tone<sup>31</sup>. Other studies suggest that ureter relaxation at the stone's site and an increase in hydrostatic pressure close to the stone brought on by the use of adrenergic antagonists and alpha channel blockers may facilitate stone transit. In numerous studies that have been published, alpha-blockers have been utilized to remove urinary calculi. The best evidence for alpha-blockers' efficacy came from the meta-analysis of these trials, which was published in 2006 by Hollingsworth and his colleagues<sup>44</sup>. In that meta-analysis, data from various trials were integrated, and the pooled risk ratio for alpha-blockers was 1.54, meaning that patients who took alpha-blockers had a 54% higher risk of passing stones than controls. Recent studies provide additional evidence for the efficiency of alpha-blockers for the surgical removal of renal stones<sup>(31)</sup>. The side effect that was reported most commonly (3.3% to 4.2%) was transient hypotension. In a later examination, Seitz and colleagues

looked at research including 2419 people. Pooling demonstrated overall advantages for stone ejection, with a relative risk of 1.45 (CI 1.34-1.57) and an absolute risk decrease of 0.27. The typical stone size varied from 4 to 7 mm. Once more, transient hypotension was the most frequently reported adverse event (3.3%–4.2%)<sup>45</sup>. The most extensively researched alpha-blocker in MET is tamsulosin. However, tamsulosin, terazosin, and doxazosin were similarly successful in expelling distal stones when compared to the control group in a randomised control trial by Yilmaz and associates. The results suggest a potential class impact, but larger research is needed to fully confirm this small-scale investigation<sup>46</sup>.

Tamsulosin's effectiveness in treating distal ureteral calculi has been confirmed by two recent randomised controlled studies, one by Al-Ansari and colleagues and the other by Kaneko and colleagues. The mean stone diameters in both studies ranged from 4.6 to 6.0 mm for the treatment (tamsulosin) and control arms. According to Al-Ansari and colleagues, the tamsulosin group had a 3.0 relative risk greater rate of stone expulsion (CI 1.152–7.45). In the Kaneko investigation, stone ejection rates of 77% in the tamsulosin group and 50% in the control arm were noted (p = 0.002)<sup>44</sup>. As a tamsulosin alternative, silodosin has drawn more and more attention. In the human isolated ureter, phenylephrine-induced ureteral contraction is mostly mediated by alpha-1A adrenoceptors<sup>(47)</sup>. Research indicate that due to the high spontaneous passing rates of smaller stones, the efficacy of stone expulsion rates for stones measuring less than 5 mm is relatively lower than for stones measuring 5 to 10 mm<sup>45</sup>.

**Calcium blockers:** The effectiveness of calcium channel blockers for the primary ejection of urinary calculi has been examined in a number of randomised controlled trials (RCTs)<sup>45,46</sup>. Also, the outcomes of these trials were combined in the meta-analysis conducted in 2006 by Hollingsworth et al.<sup>(41)</sup>. When calcium channel blockers and steroids were combined, the risk ratio for the expulsion of stones was 1:90, meaning that patients in the treatment group (calcium channel blockers/steroids) had a 90% higher chance of doing so than the control group. This conclusion was also supported by further RCTs that were published following that meta-analysis<sup>31</sup>.

It's also vital to keep in mind that several of these experiments involved kidney stones that were quite modest in size (mean stone diameter: 5 mm), despite the fact that mean stone sizes in different trials ranged from 3.86 mm to 35.93 mm. According to estimates, 15% of stones between 5 and 8 mm and 90% of stones less than 5 mm will naturally dissolve within 4 weeks<sup>(44)</sup>. Some specialists, however, believe that size is more of a medical myth than a reliable indicator of stone ejection<sup>(45)</sup>. The majority of the available data indicates that alpha-blockers and calcium channel blockers may be useful in the primary evacuation of renal and ureteric stones up to 35 mm in diameter. The only calcium channel blocker that has demonstrated some help in stone ejection is nifedipine. Nifedipine may reduce renal colic, according to studies, however it has no effect on the ejection rate of stones. According to reports, nifedipine is much less effective than alpha-blockers for easing renal colic and facilitating stone clearance<sup>47</sup>. As a result, calcium channel blockers are not advised as a monotherapy for MET in the most recent EAU guidelines. Nonetheless, because to its minor side effects, it may be used safely in combination with alpha-blockers in the right patient population.

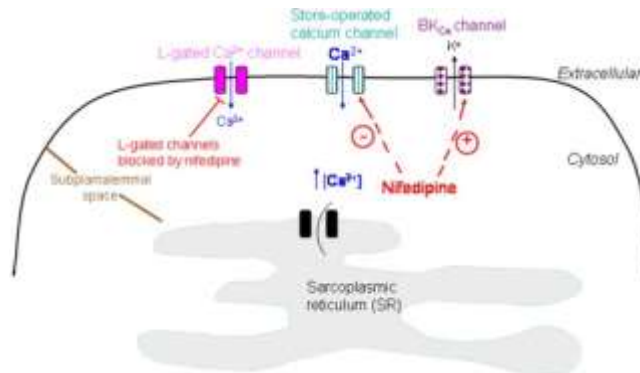
In a thorough investigation, Seitz and colleagues assessed the effectiveness of calcium channel blocker medication. 8 686 participants from 9 trials in all were examined. Those using calcium channel blockers alone had a higher rate of stone ejection compared to the control group, per pooling. As a result, the relative risk increased to 1.49 (CI 1.33-1.66) while the absolute risk decreased by 0.26. There were no major adverse effects that were reported<sup>42</sup>.

Alpha-blockers have been touted as being a more effective alternative to calcium channel blockers, despite the fact that they have demonstrated promise in distal stone evacuation. Cao and

colleagues conducted a systematic evaluation of papers directly contrasting alpha-blockers and calcium channel blockers in the treatment of lower ureteral calculi. The mean stone sizes ranged from 4.7 to 8.85 mm across 7 studies (3897 participants), all of which were published between 2004 and 2013. Tamsulosin is related with noticeably improved expulsion rates than nifedipine, according to pooled estimations, which showed a statistically significant difference between the two drugs of 0.81 (CI 0.75-0.88,  $p < 0.00001$ )<sup>48,49,50</sup>.

**Phosphodiesterase-5 inhibitors:** The use of PDE5 inhibitors in stone ejection is a novel issue in MET. Nitric oxide and cyclic guanosine monophosphate (cGMP) signalling pathways are activated by PDE5 inhibitors, increasing cGMP levels and causing smooth muscle relaxation in the ureter<sup>31</sup>. Those receiving vardenafil, sildenafil, and tadalafil saw a reduction in ureteral muscle tension; the vardenafil group saw the greatest reduction. Tadalafil in combination with tamsulosin and corticosteroid therapy was studied by Kumar and colleagues. The premise of the article was that improved ureteric relaxation and a decrease in intramural pressure may be obtained by combining medications that work via several mechanisms. There were two groups of patients. Tamsulosin 0.4 mg was administered to group 1 every day, whereas group 2 received tamsulosin 0.4 mg and tadalafil 10 mg every day. Prednisolone 5 mg/day was given to both groups for a week. Groups 1 and 2 had mean stone sizes of 7.05 mm and 6.67 mm, respectively. In group 2, stone expulsion rates increased while expulsion times reduced. The outcomes, meanwhile, did not have clinical significance. PDE5 inhibitor usage and its potential benefit in MET are still in their infancy. Further research is necessary to determine the effectiveness of PDE5 inhibitors in MET<sup>50,5</sup>.

Figure 3:



**Non-Steroidal Anti-Inflammatory Drugs:** Non-steroidal anti-inflammatory drugs provide the best analgesia in cases of renal colic because they reduce glomerular filtration, renal pelvic pressure, ureteric peristalsis, and ureteric oedema. Due to the lack of glomerular afferent arteriolar vasodilatation prevention, these patients are at risk for renal deterioration. The additional advantage of NSAIDs is that they reduce the incidence of new cases of colic and prevent hospital readmissions in the future. Despite current research supporting the use of pharmacological medicines to boost stone passage rates, NSAIDs do not appear to decrease the time to stone passage or increase the risk of stone passage in renal colic<sup>45,52</sup>.

**Mechanism of Action:** Because of their many distinctive qualities, NSAIDs are the best analgesics for renal colic. NSAIDs' main method of relieving pain in cases of renal colic is by preventing the production of prostaglandins. Local stone irritation causes prostaglandin production to increase. Prostaglandins promote glomerular afferent arteriolar vasodilatation and vascular permeability, which raises renal pelvic pressure and urine output. Use of NSAIDs slows glomerular filtration by up to 35%, lowering renal pelvic pressure and reducing stretch receptor stimulation.

Inhibiting the generation of prostaglandins also reduces ureteric oedema and inflammation, enhances drainage, and diminishes peristalsis or ureteric activity. Moreover, NSAIDs may directly relax the ureteric smooth muscle (31,52). The primary mechanism of action of NSAIDs is the inhibition of the cyclo-oxygenase (COX) enzyme, which regulates the synthesis of prostaglandins and other metabolites such thromboxanes. There are two COX isoforms; COX II is an inflammatory isoform produced at the site of inflammatory stimulation by cytokines and inflammation metabolites. An enzyme called COX I can be found in the stomach and renal blood. Even the stomach mucosa has minor levels of COX II, which is present in the majority of cells. A local inflammatory stimulus typically causes COX II to be upregulated. Many NSAIDs are available on the market; the main differences between them are the frequency and kind of side effects, particularly gastrointestinal discomfort and ulceration, renal damage, and cardiovascular implications as a result of differing degrees of cyclo-oxygenase inhibition<sup>52,53</sup>.

#### DIFFERENT TYPES OF SURGICAL PROCEDURES

**Ureteroscopy:** For the detection and treatment of disorders of the upper urinary system, ureteroscopy is a well-established minimally invasive method. It is one of the most often done surgeries in urology and the most frequently used treatment for kidney stones (55). Flexible ureteroscopy (FURS) has evolved over time into a common and effective minimally invasive surgery (MIS) procedure for both diagnostic and therapeutic operations to treat kidney and ureteral stones, strictures, and other disorders. FURS may be superior to alternative treatments such percutaneous nephrolithotomy (PCNL) and shock wave lithotripsy (SWL) in terms of stone-free rates, blood loss, length of hospital stay, and complications. However, the FURS approach requires extensive training operations on both phantoms and animals for professional capabilities because of the lengthy, narrow ureters and delicate instruments. Moreover, the prolonged standing position, the heavy load, and the immobile operating postures during surgery result in physical exhaustion and burnout for surgeons, reducing the standard of care and typical diameter of 3 mm), and delicate operational devices with only one or two degrees of freedom (with a diameter of about 1 mm) (DoFs). As a result, many robotic devices have been created specifically to target FURS. One of them, American urologist Desai, took the initiative in using the Sensei robotic system. In 2008, robot-assisted FURS and the treatment of renal calculi were carried out using a catheter system (Hansen Medical, CA, USA), which was originally created for endovascular surgery<sup>56</sup>. To perform ureteroscopy using the industry-standard Omega 3 device, a fibre endoscope and a specially designed ureteral catheter were added to this robotic catheter system (Force Dimension, Switzerland). However, the project was terminated and failed as a result of the preexisting drawbacks of a poor control method and a lack of workspace<sup>57,58</sup>.

Figure 4: Mechanism of action of non steroidal anti-inflammatory drugs<sup>51</sup>.

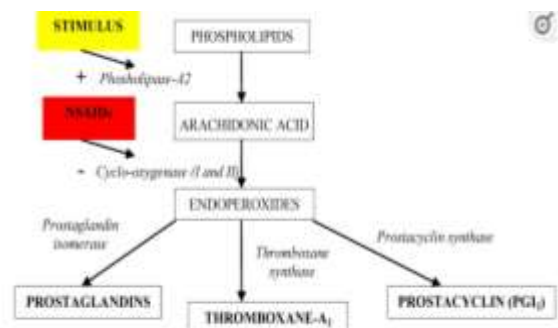




Figure 5: Operational path of FURS and its anatomy<sup>56</sup>



**Extracorporeal shock wave lithotripsy:** Extracorporeal shock wave lithotripsy (ESWL), invented by Chaussy et al. in Germany, has completely changed how kidney and urinary lithiasis are treated. Because of its noninvasive nature, low cost, high efficiency of stone disintegration, minimal exposure of patients to anaesthesia, shorter hospital stay, and fewer complications since its introduction in the early 1980s, ESWL has established itself as the first line treatment for renal stones, proximal stones, and midureteral stones<sup>59</sup>. An external power source called a lithotripter, which emits acoustic waves of high intensity and low frequency, generates the shattering forces that make up an ESWL. Every lithotripsy device consists of four components: an energy source, a focusing system, a localization unit, and a coupling mechanism. The only object of the shock waves is kidney or ureter stones. Cavitation, shear, and spilling are the key components of the fragmentation mechanism. The most significant factor thought to be responsible for breaking the stones up into smaller bits that can readily flow through the ureters is cavitation. However, for the ESWL to be as effective as possible, a number of technical considerations must be made, including the patient's energy level, the kind, size, and location of the stone, the presence of a UTI, the

frequency of the pulses, the endourologist's expertise, and prior ESWL experience. For calculi smaller than 1 cm, ESWL is regarded as the first line of treatment, per the AUA Urethral Stone Clinical Guidelines. When the stone is in the bottom pole, the ESWL's success rate drops. According to Lingeman et al. patients with lower pole calculi between 11 and 20mm and patients with calculi greater than 20 mm had stone-free rates of roughly 30% and 20%, respectively. Current research has indicated that proximal ureteral stones up to 15mm in size may benefit from ESWL<sup>59,60,61</sup>

**Percutaneous nephrolithotomy (PCNL):** Minimally invasive techniques have gained widespread acceptance and nearly completely replaced open surgery over the past 20 years. For the treatment of any stones larger than or equal to 2 cm, percutaneous nephrolithotomy (PCNL) has quickly become the norm<sup>57</sup>. The first to establish PCNL as a recognised surgical technique for removing urinary calculi, whole or in fragments, under radiological supervision was Fernstrom and Johansson in 1976. In contrast to other endoscopic operations, the risk of complications is noteworthy as being higher, especially if a surgeon has less training. The fundamental benefit of this approach is that the effectiveness of PCNL will not be impacted by the burden or composition of the stones<sup>63,64</sup>. Patients treated with PCNL have a 100% stone-free rate for stones under 10 mm, compared to 63% for patients treated with ESWL, according to Pearle et al. At the moment, people with kidney stones larger than 2 cm, lower pole stones larger than 1.0 cm, and staghorn calculi should have their stones removed percutaneously<sup>41</sup>. The procedure is done using a posterior calyx, usually in the upper or lower pole, depending on where the stone is located and how close it is to any nearby organs. Once the collecting system has been accessed, the tract leading to the renal pelvis is widened with the aid of radiological assistance. These actions are used in the case that it is not possible to remove the stone intact<sup>65,66,67</sup>.

Table 2: Characteristics of few studies included in this review

Study name	Date of publication	Journal	Country	Sampling type and size	Follow up if applicable	Study design
Mohammad et al (2014) <sup>37</sup>	2014	American ISSN	USA	Random study	Nope	Cross sectional study
Seitz et al (2009) <sup>41</sup>	2009	European urology	USA	Random study (n=47)	Nope	Qualitative study
Al-Ansari et al (2010) <sup>42</sup>	2010	Urology	USA	Random study (n=100)	Nope	Qualitative study
Dellabella et al (2005) <sup>47</sup>	2005	Journal of urology	America	Random study (n=210)	Nope	Qualitative study
Cao et al (2014) <sup>48</sup>	2014	Scientific reports	UK	Random study (n=3897)	Nope	Quantitative study
Kumar et al (2014) <sup>49</sup>	2014	Korean journal of urology	Korea	Random study (n=62)	Nope	Cross sectional study

**CONCLUSION**

Urinary calculi are included in the study along with their causes, types, pathophysiology, diagnosis, prognosis, prevention, and medical expulsion therapy. Both high urine saturation and physical and chemical changes can contribute to the development of renal stones. It has been proven that alpha-blockers and calcium channel blockers are very helpful in medical therapies for the initial evacuation of renal and ureteric stones. Different types of surgery procedures are also done to remove the stone from the urinary passage.

**Conflict of interest:** Nil

**REFERENCES**

- Zhang D, Li S, Zhang Z, Li N, Yuan X, Jia Z, Yang J. Urinary stone composition analysis and clinical characterization of 1520 patients in central China. *Scientific reports*. 2021 Mar 19;11(1):6467.
- Scales Jr CD, Smith AC, Hanley JM, Saigal CS, Urologic Diseases in America Project. Prevalence of kidney stones in the United States. *European urology*. 2012 Jul 1;62(1):160-5.
- Rule AD, Lieske JC, Li X, Melton LJ, Krambeck AE, Bergstralh EJ. The ROCKS nomogram for predicting a second symptomatic stone episode. *Journal of the American Society of Nephrology*. 2014 Dec 1;25(12):2878-86.
- Romero V, Akpınar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Reviews in urology*. 2010;12(2-3):e86.
- Khan, S. R., Pearle, M. S., Robertson, W. G., Gambaro, G., Canales, B. K., Doizi, S., ... & Tiselius, H. G. (2016). Kidney stones. *Nature reviews Disease primers*, 2(1), 1-23.

- Pearle, M. S., Goldfarb, D. S., Assimos, D. G., Curhan, G., Denu-Ciocca, C. J., Matlaga, B. R., ... & White, J. R. (2014). Medical management of kidney stones: AUA guideline. *The Journal of urology*, 192(2), 316-324.
- Shoag J, Tasian GE, Goldfarb DS, Eisner BH. The new epidemiology of nephrolithiasis. *Advances in chronic kidney disease*. 2015 Jul 1;22(4):273-8.
- Romero V, Akpınar H, Assimos DG. Kidney stones: a global picture of prevalence, incidence, and associated risk factors. *Reviews in urology*. 2010;12(2-3):e86.
- Sakhaee K. Nephrolithiasis as a systemic disorder. *Current opinion in nephrology and hypertension*. 2008 May 1;17(3):304-9.
- Uribarri J, Oh MS, Carroll HJ. The first kidney stone. *Annals of internal medicine*. 1989 Dec 15;111(12):1006-9.
- Eaton SH, Cashy J, Pearl JA, Stein DM, Perry K, Nadler RB. Admission rates and costs associated with emergency presentation of urolithiasis: analysis of the Nationwide Emergency Department Sample 2006–2009. *Journal of endourology*. 2013 Dec 1;27(12):1535-8.
- Stamatelou KK, Francis ME, Jones CA, Nyberg Jr LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976–1994. *Kidney international*. 2003 May 1;63(5):1817-23.
- Ingimarsson JP, Krambeck AE, Pais VM. Diagnosis and management of nephrolithiasis. *Surgical Clinics*. 2016 Jun 1;96(3):517-32.
- Saigal CS, Joyce G, Timilsina AR, Urologic Diseases in America Project. Direct and indirect costs of nephrolithiasis in an employed population: opportunity for disease management?. *Kidney international*. 2005 Oct 1;68(4):1808-14.
- Litwin MS, Saigal CS. Urologic Diseases in America. US Department of Health and Human Services. Public Health Service, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Washington, DC: US Government Printing Office. 2012:313-45.
- Vijaya T, Kumar MS, Ramarao NV, Babu AN, Ramarao N. Urolithiasis and its causes-short review. *J Phytopharmacol*. 2013;2(3):1-6.
- Sah K, Jauhari R. A review on kidney stones: Introduction, diagnosis and pharmacological management and future direction. *Journal of Pharmacy Research*, 2017; 11(6): 599-603.

18. Bhang S, Badarshahi D Comparison between Tamsulosin vs Tamsulosin, Deflazacort in expulsion of lower ureteric calculi. *Indian J Applied Research*, 2018; 8(10): 42-43.
19. Assimos D, Krambeck A, Miller NL, Monga M, Murad MH, Nelson CP, Pace KT, Pais VM, Pearle MS, Preminger GM, Razvi H. Surgical management of stones: American urological association/endourological society guideline, PART I. *The Journal of urology*. 2016 Oct;196(4):1153-60.
20. Türk C, Petfik A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU guidelines on diagnosis and conservative management of urolithiasis. *European urology*. 2016 Mar 1;69(3):468-74.
21. Bacchus MW, Locke RA, Kwenda EP, DeMarco RT, Grant CM, Bayne CE. Medical Expulsive Therapy (MET) For Ureteral Calculi in Children: Systematic Review and Meta-Analysis. *Frontiers in Urology*.:8.
22. Lu Z, Dong Z, Ding H, Wang H, Ma B, Wang Z. Tamsulosin for ureteral stones: a systematic review and meta-analysis of a randomized controlled trial. *Urologia internationalis*. 2012;89(1):107-15.
23. Almannie RM, Al-Nasser KA, Al-Barraq KM, Alsheheli MM, Al-Hazmi HH, Binsaleh SA, Althunayan AM, Alomar MA. The effect of the body mass index on the types of urinary tract stones. *Urology annals*. 2020 Jan;12(1):42.
24. Ma Q, Fang L, Su R, Ma L, Xie G, Cheng Y. Uric acid stones, clinical manifestations and therapeutic considerations. *Postgrad Med J*. 2018 Aug;94(1114):458-462.
25. Trinchieri A, Montanari E. Prevalence of renal uric acid stones in the adult. *Urolithiasis*. 2017 Dec;45:553-62.
26. Parkhomenko E, De Fazio A, Tran T, Thai J, Blum K, Gupta M. A Multi-Institutional Study of Struvite Stones: Patterns of Infection and Colonization. *J Endourol*. 2017 May;31(5):533-537.
27. Hoffman A, Braun MM, Khayat M. *Kidney Disease: Kidney Stones*. FP essentials. 2021 Oct 1;509:33-8.
28. Izzedine H, Lesecure FX, Bonnet F. HIV medication-based urolithiasis. *Clin Kidney J*. 2014 Apr;7(2):121-6.
29. Samantha C, Avani S, Kumar E, Prasobh G. A review on urinary calculi-types, causes, its mechanism, diagnosis, prevention and medical expulsion therapy of calculi. *World Journal of Pharmaceutical Research*. 2021 May 27;9(10):473-86.
30. Gottlieb M, Long B, Koyfman A. The evaluation and management of urolithiasis in the ED: A review of the literature. *The American journal of emergency medicine*. 2018 Apr 1;36(4):699-706.
31. Wang Z, Zhang Y, Zhang J, Deng Q, Liang H. Recent advances on the mechanisms of kidney stone formation. *International journal of molecular medicine*. 2021 Aug 1;48(2):1-0.
32. Quhal F, Seitz C. Guideline of the guidelines: urolithiasis. *Current opinion in urology*. 2021 Mar 1;31(2):125-9.
33. Shadman A, Bastani B. *Kidney Calculi: Pathophysiology and as a Systemic Disorder*. *Iran J Kidney Dis*. 2017 May;11(3):180-191.
34. Tsujihata M. Mechanism of calcium oxalate renal stone formation and renal tubular cell injury. *International Journal of Urology*. 2008 Feb;15(2):115-20.
35. Campschroer MT, Zhu X, Vernooij R, Lock T. Re: What is the Role of  $\alpha$ -Blockers for Medical Expulsive Therapy? Results From a Meta-analysis of 60 Randomized Trials and Over 9500 Patients. *Urology*. 2019 Jun;128:112-3.
36. Türk C, Petfik A, Sarica K, Seitz C, Skolarikos A, Straub M, Knoll T. EAU guidelines on diagnosis and conservative management of urolithiasis. *European urology*. 2016 Mar 1;69(3):468-74.
37. Mohammad HR, Kamal YM, Abdul-Kareem NF. Effect of Tamsulosin on calculus clearance after extracorporeal shock wave lithotripsy in patients with Renal Stone: a randomized, placebo-controlled study. *American ISSN: s. com journal-www. usa*. 2014:59-49.
38. Sio MD, Autorino R, Lorenzo GD, Damiano R, Giordano D, Cosentino L, Pane U, Giacomo FD, Mordente S, D'Armiendo M. Medical expulsive treatment of distal-ureteral stones using tamsulosin: a single-center experience. *Journal of endourology*. 2006 Jan 1;20(1):12-6.
39. Parsons JK, Hergan LA, Sakamoto K, Lakin C. Efficacy of  $\alpha$ -blockers for the treatment of ureteral stones. *The Journal of urology*. 2007 Mar 1;177(3):983-7.
40. Al-Ghamdi MA, Abdulkadir A. Medical therapy for primary expulsion of urinary calculi: A review. *Sub-Saharan African Journal of Medicine*. 2017 Oct 1;4(4):91.
41. Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zwergel U. Medical therapy to facilitate the passage of stones: what is the evidence?. *European urology*. 2009 Sep 1;56(3):455-71.
42. Al-Ansari A, Al-Naimi A, Alobaidy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. *Urology*. 2010 Jan 1;75(1):4-7.
43. Kaneko T, Matsushima H, Morimoto H, Tsuzaka Y, Homma Y. Efficacy of low dose tamsulosin in medical expulsive therapy for ureteral stones in Japanese male patients: a randomized controlled study. *International journal of urology*. 2010 May;17(5):462-5.
44. Shafi H, Moazzami B, Pourghasem M, Kasaeian A. An overview of treatment options for urinary stones. *Caspian journal of internal medicine*. 2016;7(1):1.
45. Al-Ghamdi MA, Abdulkadir A. Medical therapy for primary expulsion of urinary calculi: A review. *Sub-Saharan African Journal of Medicine*. 2017 Oct 1;4(4):91.
46. Moynihan AT, Smith TJ, Morrison JJ. The relaxant effect of nifedipine in human uterine smooth muscle and the BKCa channel. *American journal of obstetrics and gynecology*. 2008 Feb 1;198(2):237-e1.
47. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of Tamsulosin, Nifedipine and Phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol* 2005;174:167-72.
48. Cao D, Yang L, Liu L, Yuan H, Qian S, Lv X, Han P, Wei Q. A comparison of nifedipine and tamsulosin as medical expulsive therapy for the management of lower ureteral stones without ESWL. *Scientific reports*. 2014 Jun 11;4(1):1-5.
49. Kumar S, Jayant K, Agrawal S, Singh SK. Comparative efficacy of tamsulosin versus tamsulosin with tadalafil in combination with prednisolone for the medical expulsive therapy of lower ureteric stones: a randomized trial. *Korean journal of urology*. 2014 Mar 1;55(3):196-200.
50. Gratzke C, Uckert S, Reich O. PDE-5-Inhibitoren: Ein neuer Therapieansatz in der Behandlung der Harnleiterkolik?. *Der Urologe*. 2007;46:1219-23.
51. Jäger T, Mokos A, Prasianakis NI, Leyer S. first\_page settings Order Article Reprints Open AccessArticle Pore-Level Multiphase Simulations of Realistic Distillation Membranes for Water Desalination. *Membranes*. 2022. Davenport K, Waiane E. The role of non-steroidal anti-inflammatory drugs in renal colic. *Pharmaceuticals*. 2010 Apr 28;3(5):1304-10.
52. De Coninck V, Keller EX, Somani B, Giusti G, Proietti S, Rodriguez-Socarras M, Rodriguez-Monsalve M, Doizi S, Ventimiglia E, Traxer O. Complications of ureteroscopy: a complete overview. *World journal of urology*. 2020 Sep;38:2147-66.
53. Zhao J, Li J, Cui L, Shi C, Wei G. Design and performance investigation of a robot-assisted flexible ureteroscopy system. *Applied bionics and biomechanics*. 2021 Nov 18;2021.
54. Zhao J, Wang S, Wang J, Li J, Cui L, Li J. Design and experiment of a 3- DoF master device with a 2- DoF parallel mechanism for flexible ureteroscopy. *The International Journal of Medical Robotics and Computer Assisted Surgery*. 2023 Feb;19(1):e2459.
55. Lildal SK, Osther P, Jung H. Irrigation Mechanisms and Intrarenal Pressure in Flexible Ureteroscopy. In *Flexible Ureteroscopy 2022* Sep 16 (pp. 99-115). Singapore: Springer Nature Singapore.
56. Li K, Lin T, Zhang C, et al. Optimal frequency of shock wave lithotripsy in urolithiasis treatment: a systematic review and meta-analysis of randomized controlled trials. *J Urol* 2013; 190: 1260-7.
57. Alaneer S, Ugarte R, Monga M. The effectiveness of shock wave lithotripters: a case matched comparison. *J Urol* 2010; 184: 2364-7.
58. Ziaee SA, Halimiasl P, Aminsharif A, Shafi H, Beigi FM, Basiri A. Management of 10–15-mm proximal ureteral stones: ureteroscopy or extracorporeal shockwave lithotripsy?. *Urology*. 2008 Jan 1;71(1):28-31.
59. Kamal W, Kallidonis P, Kyriazis I, Liatsikos E. Miniturized percutaneous nephrolithotomy: what does it mean?. *Urolithiasis*. 2016 Jun;44(3):195-201.
60. Pearle MS, Nadler R, Bercowsky E, et al. Prospective randomized trial comparing shock wave lithotripsy and ureteroscopy for management of distal ureteral calculi. *J Urol* 2001; 166: 1255-60.
61. Preminger GM, Assimos DG, Lingeman JE, et al. Chapter 1: AUA guideline on management of staghorn calculi: diagnosis and treatment recommendations. *J Urol* 2005; 173: 1991-2000.
62. Zeng G, Wan S, Zhao Z, Zhu J, Tuerxun A, Song C, Zhong L, Liu M, Xu K, Li H, Jiang Z. Super- mini percutaneous nephrolithotomy (SMP): a new concept in technique and instrumentation. *Bju International*. 2016 Apr;117(4):655-61.
63. Shah K, Agrawal MS, Mishra DK. Superperc: A new technique in minimally-invasive percutaneous nephrolithotomy. *Indian Journal of Urology: IJU: Journal of the Urological Society of India*. 2017 Jan;33(1):48.
64. Kallidonis P, Kyriazis I, Kotsiris D, Koutava A, Kamal W, Liatsikos E. Papillary vs nonpapillary puncture in percutaneous nephrolithotomy: a prospective randomized trial. *Journal of endourology*. 2017 Apr 1;31(S1):S-4.
65. Mehta TH, Goldfarb DS. Uric acid stones and hyperuricosuria. *Advances in chronic kidney disease*. 2012 Nov 1;19(6):413-8.
66. Türk C, Petfik A, Sarica K, et al. EAU Guidelines on Interventional Treatment for 469 Urolithiasis. *Eur Urol*. 2016 Mar;69(3):475-82.
67. Gottlieb M, Long B, Koyfman A. The evaluation and management of urolithiasis in the ED: A review of the literature. *The American journal of emergency medicine*. 2018 Apr 1;36(4):699-706.