



## A REVIEW ON UROLITHIASIS

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### ABSTRACT:

Urolithiasis is the urinary disorder characterized by formation of stone in the urinary tract, urinary bladder and kidneys. Urolithiasis is considered to be a risk of urinary incontinence and may be associated with urinary incontinence. A urinary stone commonly occurs in males and are calculated on the basis of their mineral composition. Approximately 80% of urinary stones composed as calcium oxalate and calcium phosphate. Urinary calculi can cause disruption to the urinary system, hydrophoresis, infections and bleeding. Root stone formation is the result of several mechanisms. Whereas exceeding supersaturation (i.e. free stone formation) is the cause of uric acid or cystine calculi, infection stones result from bacterial metabolism. Renal calculi can be broadly classified in two large groups: tissue attached and unattached.

Components in diet increase the risk of stone formation include low intake of fluid and animal protein, sodium, sugar and syrup high corn fruit, oxalate, grape juice, apple juice and cola drinks.

Vegetarian diets, spices and liquids may be helpful in treating and prevention and kidney stones. Therefore, the best way to prevent kidney stones is to consume a lot of water and a magnesium rich vegan. Common medications used to prevent urolithiasis do not work for all patients, and many have adverse effects that endanger their long-term use.

Managing today's urolithiasis with open renal surgery is unusual and rarely used, only by the introduction of Extracorporeal Shock wave lithotripsy (ESWL) is useful but it is expensive.

Herbs and herbal medicines have created interest among people with its clinically proven effects such as immunomodulation and antimutagenic. Also, abusing synthetic drugs due to serious side effects of the drug has allowed humans to return to nature for safe treatment.

**Key words:** hydrophoresis, Urolithiasis

### INTRODUCTION:

Urolithiasis is a urinary incontinence characterized by a buildup of stones in the urinary tract, urinary bladder and kidneys. Urolithiasis commonly occurs in men. Urinary stones can cause damage in bladder, ureters, or kidney failure, severe painful episodes.

Stones are mainly made up of minerals like calcium, magnesium, phosphate and others. Urolithiatic stones are based on mineral composition. The only stones are struvite (calcium carbon dioxide), calcium oxalate, urate, cystine and silica.

The most common type of kidney stones worldwide contains calcium. Preventative measures depend on the type of stones.

Urolithiasis affects 12% of the global population and mortality rates of men from 70-81% and 47-60% in women. The future ridge location is a little south compared to other areas. The occurrence of kidney stones in the southern part is lower than in other sections.

The rate of urolithic stones is three times higher than in men that of women at the time of exposure to testosterone and estrogen that prevents the formation of the stone. (2)

The structure of the renal stone and the basic chemical composition of the renal stone depend on age and sex. Most stones are present in older patients. However, clinical findings have shown that not only are changes in urine and calcium metabolism, but also changes in sex and age.

Although some authors have suggested that climate change is a concern, biological and nutritional changes are the cause of urolithiasis and growth.

Urinary stone disease still rare in children with stable overall incidence in most series. As in adults, factors involved in metabolic syndrome such as obesity pose a risk for urinary stones in children (3)

About 80% of these calculations consist of calcium oxalate and calcium phosphate. Urinary stones can cause rupture, hydronephrosis, infection and hemorrhage in the urinary system. Surgery, lithotripsy, and localized laser abnormalities have been widely used to remove calculi.

However, these procedures are very expensive and with these procedures the recurrence is very common. The relapse rate without preventative treatment is approximately 10% at 1 year, 33% at 5 years and 50% at 10 years. (4)

### **Pathogenesis and pathophysiology**

The formation of urinary stones is the result of various mechanisms. Since super-saturation (i.e., free stone formation) is the cause of uric acid or cystine calculi, stones of infection are the result of bacterial metabolism.

The formation of the most general fraction, calcium-containing stones are more complex and not yet fully understood. Recent evidence suggests that it is possible to form a free and fixed stone.

The long-accepted simple explanation for overcoming the dissolution of solvents of lithogenic substances in the urine cannot adequately describe these complex processes.

They deviate from the hypothesis that initial crystal deposition occurs in the lumen of the kidney tubules, new discoveries suggest the formation of basal plaques in the interstitial space of the renal papilla.

Calcium phosphate crystals and the organic matrix initially precipitate along the membranes of the lower layer of Loop of Henle and extend into the interstitial space to the urethra, forming Randall plaques that are regularly found during the endoscopy of patients who form calcium oxalate stones.

These calcium phosphate crystals of calcium plaque in addition to urine calcium in the matrix formed by linking molecules and the molecules can say that it is the source of one of the stones of development. Actuators, the mechanisms of full physicality involved, as well as matrix molecules, are still unknown. (3)

### **Types of Urolithiasis**

Renal calculi can be broadly classified in two large groups: tissue attached and unattached.

The stones are mainly combined with a calcium monohydrate (COM) calcium stone, and the kidneys have a detectable connective site to the papilla, consisting mainly of a core set of peripheral layers of concentrated chips near the junction site (concave area) and radially planed.

A non-attached calculi, without the location where papilla ligaments are detected, develops the renal cavity with a low or reduced urodynamic effect and can show different composition and structures. A number of reports have been published since the first report on papillary calibration and the active role it can play in papillary calculi bondage. (4)

The type of stone is named for its mineral composition. The most common stones are struvite (magnesium ammonium phosphate), calcium oxalate, urate, cystine and silica.

### **TYPES OF STONES**

Some types of kidney stones have a combination and pathogenesis. The stone species are named for their mineral composition. These chemicals are part of normal human nutrition and are important parts of the body such as bones and muscles.

#### **1. Calcium stones**

Most kidney stones are calcium stones, which are mixed with oxalate, phosphate or sometimes uric acid. The crystal structure of calcium oxalate is also one of the toxic effects of ethylene glycol toxicity. Oxalate is a natural substance found in foods. Some fruits, vegetables, nuts and chocolate have a high level of oxalate.

The liver also produces oxalate. Nutritional factors, excessive vitamin D intake, participation in surgery, and many life-threatening problems can increase urinary calcium or oxalate concentrations.

All calcium stones are radio-opaque, and calcium oxalate and calcium phosphate stones are black, gray or white and small (about 1 cm in diameter) and are easily updated on radiographs. Calcium oxalate stones are commonly seen as 'envelope' under a microscope.

Calcium phosphate levels are associated with conditions such as hypothyroidism and tubular acidosis.

## 2. Uric acid stones

Uric acid stones are smooth, round, yellow-orange and nearly radiographically transparent. About 5–10% of all stones are formed from uric acid.

Uric acid stones can form in people who don't drink enough fluids or who lose too much fluid, those who eat a high-protein diet, diets high in purines, especially those containing meats and fish and those who have gout certain metabolic abnormalities; including obesity or certain genetic factors also may increase your risk of uric acid stones<sup>18</sup>.

These patients also have a tendency to form urate stones.

Urate stones are especially common after colon resection.

Uric acid crystals appear as crystalline crystals, usually in bats, squares or diamonds.

## 3. Struvite or infection or triple phosphate stones

Struvite is a crystalline substance containing ammonium phosphate. About 10-15% of the calculus is struvite. Struvite stones are most likely to be infected by the deadly bacteria in urea.

These bacteria convert urea into ammonia and CO<sub>2</sub> in presence of urease enzyme. The ammonia is responsible for alkalisation of urine. Alkaline urine is suitable condition for synthesis of struvite calculi. It is a common metabolic disorder in studies such as idiopathic hypercalcemia, hyperparathyroidism and gout.

The stones are large, deformed and perforated. These stones can grow very fast and very large, sometimes with little or no warning sign. Symptoms of stone structures are higher than urine pH 7, and bacteria that grow in culture under conditions of urease (proteus, klebsiella, pseudomonas).

## 4. Protease-related stones

It is a very new stone. Excessive use of Protease inhibitors such as indinavir sulfate in anti- HIV therapy may lead to formation of stones. In this therapy, about 4 to 12% of patients may lead to formation of stones.

## 5. Cystine stones.

These stones are less common in community. These are basically found in genetic disorders. High amount of certain amino acids are excreted in this condition known as cystinuria. It is an inherited autosomal urinary recessive disorder which may cause urolithiasis in kidneys, bladder and urethra. Urinary stone formation takes place when urinary excretion of insoluble cystine is more than 600mg per day. Morphologically stones are greenish yellow in colour and radio opaque, round in shape.

## 6. Silicate stones or drug induced stones

These stone mostly drug induced. Certain drugs such as furosemide, carbonic anhydrase inhibitors, ephedrine, guaifenesin, indinavir, triamterene antibiotics such as ciprofloxacin, Sulphonamides and silica containing substances causes deposition of silicate and leads to formation of silicate stones. Abused laxatives may also cause silicate stones (26)

Renal silicate calculi are less common, occurs less than 1% of all urinary calculi in humans. Several case reports showing that the long-term uses of magnesium trisilicate induced silica renal calculi.

**Table 1:** Common composition and approximate incidences of renal stones are given below

S. No	Name of stone	Approximate incidence	Constituents
1.	Calcium oxalate	70 % of all stones	Calcium, oxalate
2.	Calcium phosphate	10 % of all stones	Calcium, phosphate
3.	Uric acid	5-10 % of all stones	Uric Acid
4.	Struvite	10 % of all stones	Calcium, ammonia, phosphate
5.	Cystine	Less than 1% of all stones	Cystine

### Causes of urolithiasis

Inadequate intake of water is common cause of formation of stones. Apart from that high intake of animal proteins, sodium, refined sugars, oxalate containing drinks, some fruit juices such as apple, grape juice; are the common causative factors of stone formation. Urinary stone formation also due to decrease in urine formation and therefore decrease in urinary output.

Decrease in urinary output may be due various underlying factors including infection in urinary tract, excess dietary stone forming elements, deficiency of vitamin A or excess vitamin D. Vitamin abnormalities usually arise in underlying metabolic abnormal conditions such thyroid disorders, hepatic disorders and GI disorders. The main constituents of kidney stone are calcium oxalate. The formation of stone takes place concentrating these elements in urine and supersaturation of urine. (5)

### Supersaturation of urine

Supersaturation of urine is the condition when the urine solvent contains more crystal forming substances that it can hold in solution. After the urine turns into supersaturated the nucleation process starts in which seed crystal form. There are two ways of nucleations; heterogeneous and homogenous. In heterogeneous nucleation process solid surface present and crystals can grow at the solid surface, this takes less time to grow. In other hand homogenous nucleation crystal grow in liquid medium. Homogenous nucleation requires less energy and grows comparatively slowly.

Seed crystal adheres to renal papilla or wall of bladder, forms aggregates and become larger stone. The rate of stone formation depends on chemical composition of stones and abnormal urine pH. (5, 3)

Supersaturation of the urine depends on calculogenic compound and pH-dependent. For example, at a pH of 7.0, the uric acid solubility in urine is 158 mg/100 ml and at the pH % the solubility of uric acid is less than 8 mg/100 ml which may leads to formation of stone. Usually uric acid stones forms along with hyperuricosuria and low urine pH.

Supersaturation is likely the underlying cause of uric acid and cystine stones, but calcium-based stones (especially calcium oxalate stones) may have a more complex etiology.(5)

### Signs and symptoms of urolithiasis

Small size stones may pass through or impact the ureters and damage the linings of ureters; this may cause hematuria (blood in urine). These calculi cause clog in ureters. Ureters get spasm due to obstruction; therefore acute intermittent ischemic pain (*renal colic*) occurs. Small size stones reaching the bladder may be passed in urine and large size stones cannot pass therefore obstruct the urethra or bladder.

Clinical manifestations of urolithiasis are urinary retention and bilateral hydronephrosis, renal infections, pyelonephritis and kidney failure.

Other sign and symptoms includes Nausea, vomiting, Hematuria, pyuria, Dysuria, Oliguria, pain and frequent urination

### Large calculi (staghorn calculus)

Large calculi develops slowly usually take many years for develop. It causes filling the renal pelvis and the calyces. This is due to infections, hydronephrosis and kidney tumours. It causes chronic kidney failure.

### Diagnosis of urolithiasis

The primary diagnosis of renal calculi is based on common signs and symptoms such as hematuria, polyuria, oligouria, dysuria or acute renal pain. According to severity of signs and symptoms the further diagnosis of urolithiasis is carried out.

Imaging techniques such as X-ray, computed tomography, ultra-sound are employed to confirm the urolithiasis. Apart from that various test also performed to detect the possible causes and underlying mechanism.

Microscopic study of urine is helpful to detect the Proteins, RBC, bacteria or other micro-organisms, cellular casts and crystals.

Urine culture is also helpful tool to detect the type of bacterial infection.

Hematological tests such as blood count or renal function tests also performed. Raised WBC count

indicates the presence of infection and abnormal raised blood calcium level also suggests the presence of stones.

### Management & Advancements of therapy

Usually physicians are not treated in primary stage of kidney stones; they just suggested some pain killers to relieve the pain until the stones pass out their own.

Urolithiasis can be prevented by diet control. Vegetarian diet, green leafy vegetables, liquids and intake of plenty of water helpful in prevention of kidney stones.

Calcium stones are generally treated with potassium citrate and diuretics. The uric acid stones are treated with allopurinol, which decreases the high level of uric acid in the body along with potassium citrate. Antibiotics are given to manage struvite stones. Cystine stones are treated with mercaptopropionyl glycine and potassium citrate.

Drugs used to prevent urolithiasis are not effective in all patients and also cause a lot of side effects. Therefore these drugs cannot be used for long time.

Open renal surgery is another option to treat urolithiasis but now a days not used. Instead of open renal surgery, urolithiasis is managed by Extracorporeal Shock Wave Lithotripsy (ESWL) which has almost become the standard procedure for eliminating kidney stones.

Shock waves cause traumatic effect in the renal pelvis and some stone fragments may remains in kidneys, resulting in acute renal injury and increase the stone recurrence. ESWL is relatively costly procedure, so all patients cannot afford. (6)

However; these treatments are relatively costly, painful and require expert hands with availability of appropriate equipments. So it is become important to stimulate research on traditional medicines showing anti-urolithiatic activity. Many herbs are reported to have anti-urolithic spectrum and known to decrease the formation of kidney stones. These drugs reported as lesser side effects; hence the search for antilithiatic drugs to be effective without side effects from natural sources has gained great potential. (8)

Herbal drugs have many advantages over synthetic drugs. Herbal drugs are safer drugs and commonly have immune-modulatory, anti-mutagenic property. In other hand long term use of synthetic drugs may lead to many side effects. This creates focus on herbal drugs to treat urolithiasis.

The origins, according to many, can be sourced to the World Health Organization's Canberre conference in 1976, which promoted the concept of 'Traditional' medicines for the developing countries. It has shown that lower intake of inferior quality proteins and high animal proteins increase the stone formation. Urolithiasis is more common in northern India as compared to southern India. It is also observed that high wheat diet increases the stone formation. People living in rocky areas, where the climate is hot and dry, seem to be more to urinary calculi disease. (7)

The recurrence rate is approximately 50% without preventive treatment which creates its need. Long term use of drugs produces various side effects such as hemorrhage, High BP, kidney failure etc.

For advancement of therapy, it is clear indication for explore new medicines. In Ayurveda ancient remedies have proven anti-urolithic effects and most of them derived from plants origin. In sequence of this herbal remedies has assumed to have great anti-urolithic spectrum.

Various families of plants having anti-urolithic activities are Apocynaceae, Asparagaceae, Aspleniaceae, Asteraceae, Boraginaceae, Pedaliaceae, Periplocaceae, Tropaeolaceae, Malvaceae, Meliaceae, Polygonaceae, Moraceae, Myrtaceae, Nyctaginaceae, Zingiberaceae, Liliaceae, Lythraceae, Euphorbiaceae etc. (29)

Various plant of these families decreases the recurrence rate of formation of stones with lesser adverse effects. However, the scientific documentation of their use is not well established through systematic scientific documentation making it worthwhile to explore.

As per the indigenous system of medicine, the various citrus species such as citrus medica, citrus Limon, citrus aurantium etc. have been traditionally claimed for their Antiurolithic activities.

Citrus species were used in traditional practices as remedies for the urolithiasis have been well established in vivo-vitro test, clinical trial and effective use but are lacking well documented record. (13)

### References

1. Kishor R. N, Mangilal T, Anjaneyulu N. Abhinayani G. Sravya N. ;Investigation of Antiurolithic activity of brassica oleracea gongyloides and Demostachya bipinnata in experimentally induced urolithiasis in animal models; *International journal of pharmacy and pharmaceutical sciences*; 2014;Vol. 6(6); 602-4
2. Knoll T. ; Epidemiology, Pathogenesis, and Pathophysiology of Urolithiasis; *European urology supplements*; 2010;9: 802-6
3. Patel R K, Patel S B, shah J G; Anti-Urolithiatic Activity of Ethanolic Extract of Seeds of Benincasa Hispida ; *Pharmacologyonline*;2011 3: 586-591
4. Tiwari A, Soni V, Lodhe V, Bhandarkar A, Bandawane D, Nipate S; An overview on potent indigenous herbs for urinary tract infirmity: Urolithiasis ; *Asian Journal of Pharmaceutical and clinical research*;2012; Vol.5 (1); 7-12
5. Vijaya T, Sathish M, Ramarao N. V., Naredra Babu A., Ramarao N.; Urolithiasis and Its causes- Short review ; *The general of phytopharmacology*;2013; 2(3): 1-6
6. Mikawlawng K, kumar S, Vandana; Current scenario of urolithiasis and the use of medicinal plants as antiurolithiatic agents in Manipur (North East India): A Review; *Interanational journal of herbal medicine*;2014; 2(1); 1-12
7. Ahmed S, Hasan M M, Alam Z, Mahmood; In vitro urolithiasis models: An evaluation of prophylactic management against kidney stones; *Journal of Pharmacognosy and Phytochemistry*2016; 5(3): 28-35
8. Saxena N, Argal A; Study of antiurolithiatic activity of a formulated herbal suspension; *Herba Polonica, fron botanical to Medical research*2015; 61(2): 41-49
9. Patel S, Raval S, Prajapati A; Effect of citrus medica britt. Extract on serum Biochemical changes in ethylene glycol Induced renal damage in wistar rats; *Explor Anim Med Res*;2015 Vol.5, Issue - 2, 2015, p. 202-206
10. Dosoky N S, Setzer W N; Biological Activities and Safety of Citrus spp. Essential Oils;*Int. J. Mol. Sci.*2018, 19, 1966
11. Shah A P, Patel S B, Patel K B, and Gandhi T R; Effect of Citrus Medica Linn. in Urolithiasis Induced by Ethylene Glycol Model; *Iranian journal of pharmacology & therapeutics*; 2014; vol. 13(1); 35-39
12. Atul K. Sohgaura, Bigoniya P, Shrivastava B; In Vitro Antilithiatic Potential of Kalanchoe pinnata, Emblica officinalis, Bambusa nutans, and Cynodon dactylon; *Journal of Pharmacy & Bioallied Sciences*; 2018; Vol 10 (2); p. 83-89
13. Vivek K, Ujwal K, Dharmendra M, Rajesh M; Inhibition of renal calculi formation by citrus decumana fruit extract on ethylene glycol and ammonium chloride induced urolithiasis rat model; *Indo-global research journal of Pharmaceutical sciences*; 2013; 3(2); p2-5
14. Al-Yahya M A, Mothana R A, Al-Said M S, Al-Dosari M, Al-Sohaibani M, Parvez M K, Rafatullah S; Protective effect of citrus medica 'otroj' extract on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney; *Digest Journal of Nanomaterials and Biostructures* Jan - Mar 2015,Vol. 10, No. 1, p. 19 – 29
15. Bawari S, Archana N. S, Tewari D; In Vitro Antiurolithiatic Activity of Citrus jambhiri Lush; *Annual conference of Indian Pharmacological Society, Chandigarh* 2016; IND 7
16. Touhami M, Laroubi A, Elhabazi K, Loubna F, Zrara I, Eljahiri Y, Oussama A, Grases F and Chait A; Lemon juice has protective activity in a rat urolithiasis model; *BMC Urology*;2007;7:18
17. Sudha S R, Suresh P, Murugesan M and Manickavasagam K; Anti urolithiatic activity of a siddha herbomineral drug by zinc implantation method in experimental rats; *World Journal of Pharmaceutical Sciences*; 2016; 4(8): 233-244
18. Shukla A K, Shukla S, Garg A, Garg S; A Review On Anti-Urolithiatic Activity Of Herbal Folk Plants; *Asian Journal of Biomaterial Research*;2017; 3(2): 1-11
19. Butterweck V, Khan SR. Herbal Medicines in the Management of urolithiasis: Alternative or Complementary? *Planta Med*; 2009; 75: 1095–1103
20. Akila L, Kumar P A and Nirmala P; Effect of a polyherbal formulation on ethylene glycol Induced urolithiasis; *International Journal of Pharma and Bio Sciences*;2011; 2(4) p 7-24
21. Ullah N, Khan A M, Khan T and Ahmad W; Nephroprotective potentials of Citrus Aurantium: A prospective pharmacological study on experimental models; *Pak. J. Pharm. Sci.*, May 2014,Vol.27, No.3, pp.505-510

22. Sridharan B, Michael S T, Arya R, Roopan S M, Ganesh R N, and Viswanathan P; Beneficial effect of Citrus limon peel aqueous methanol extract on experimentally induced urolithic rats; *Pharmaceutical Biology*, 2016 Vol. 54, No. 5, 759–769
23. Gilhotra U K, Christina A.J.M.; Effect of *Rotula aquatica* Lour. on ethylene-glycol induced urolithiasis in rats.; *Int. J. Drug Dev. & Res.*, Jan-March 2011, 3 (1): 273-280
24. Nagal A, Singla RK ; Herbal Resources with Antiuro lithiatic Effects: A Review; *Indo Global Journal of Pharmaceutical Sciences*; 2013; 3(1): 6-14
25. Gilhotra UK, Mohan G, Christina AJM; Antilithiatic activity of poly-herbal formulation tablets by in-vitro method; *Journal of Applied Pharmaceutical Science*; May, 2013; Vol. 3 (05), p. 043-048
26. Arya P, Pandey S, Verma V; Kidney stones formation and use of medicinal plants as Antiuro lithiatic agents; *Universal Journal of Pharmaceutical Research*; 2017; Vol.2(2); 42-48
27. VBR Gouru, SP Vaddi, SR Dadireddy, S Gnanaguruswamy; Renal silica calculi in children: Report of two cases and review of literature; *Archives of International Surgery*; 2015; Vol 5(2); 117-119
28. Anne Waugh & Allison Grant; Intake of raw materials and elimination of waste: The urinary system chapter 13; *Ross & Wilson anatomy & Physiology in health and Illness*; 12<sup>th</sup> edition; 2014; page-354
29. Ahamd S, Ahsan I, Hasan MM; Exploring globally used antiuro lithiatic plants of A to L
30. Families: Asteraceae, Fabaceae and Lamiaceae revisited; *Journal of Pharmacognosy and Phytochemistry* (2017); 6(5): 1780-1787