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Non Surgical or Medical Management of Uretric Stone: A Review

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ABSTRACT:
Uretric stone is a significant global trouble faced with increasing prevalence everyday affecting 5-15% of the population. Acute renal colic, a regular symptom is seen. No any specific cultural, racial groups or geographical factors responsible for this ailment. Recurrence rates are close to 50%and cases of urolithiasis are still increasing massively. Pharmacologic intervention is effective in controlling the pain of kidney stones, interfere in lithogenesis process and contribute for removal. Recurrent stone formation can be prevented by the use of reasonable dietary and fluid recommendations and directed pharmacologic intervention. Calcium-sparing diuretics such as thiazides are also used for its treatment. Citrate medications increase levels of this naturally occurring stone inhibitor. There are several herbal formulations used affluently for preventing recurrence stone formation. In this review article, we provide an update on the non-surgical treatments of stone disease, focusing our attention on what is known and what is new in kidney stone management. As the affected population is getting younger and recurrence rates are high, dietary modifications, lifestyle changes and medical management are essential.
Key words: Uretric stone, non-surgical therapy, fluid intake therapy, diuretic therapy, herbal therapy, probiotic therapy and expulsive therapy

INTRODUCTION:

Since ancient times the uretric stones (urolithiasis) are well known, mainly consisting of calcium salts, uric acid, cysteine, and struvite.[1] Calcium oxalate and calcium phosphate are the most

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common types accounting for >80% of stones, followed by uric acid (8–10%) and cysteine, struvite in individuals. The occurrence is increasing world wide, with geographic, racial and gender variation. Family history reports, young age at onset, recurrent urinary tract infections (UTIs) and underlying diseases like renal tubular acidosis (RTA) and hyperparathyroidism are the major risk factors for recurrence. High incidence and recurrence rate add enormous cost and loss of work days. Though the pathogenesis of stone disease is not fully understood, systematic metabolic evaluation, medical treatment of underlying conditions and patient-specific modification in diet and lifestyle are effective in reducing the incidence and recurrence of stone disease.[2]

EPIDEMIOLOGY:

Prevalence of urinary calculi is estimated to be 5% in the general population, with an annual incidence of as much as 1%.[3] Men are twice as likely as women to develop calculi, with the first episode occurring at an average age of 30 years. Women have a bimodal age of onset, with episodes peaking at 35 and 55 years. Without preventive treatment, the recurrence rate of calcium oxalate calculi increases with time and reaches 50% at 10 years.[4]

PATHO-PHYSIOLOGY:

Uretric stones are crystalline mineral deposits, developed from microscopic crystals in the loop of Henle, the distal tubule or the collecting duct and enlarges to form visible fragments.[4]This mechanisn of stone formation depends on urinary volume with concentrations of calcium, phosphate, oxalate, sodium and uric acid ions, concentrations of natural calculus inhibitors (e.g., citrate, magnesium, Tamm-Horsfallmucoproteins, bikunin) and urinary pH.[5] High ion levels, low urinary volume, low pH, and low citrate levels favor calculus formation.

TYPES OF URETRIC STONES :

Uretric stones are made of organic and inorganic crystals intermixed with proteins. Calcium stones are the most frequent type, accounting for up to 80% . Of these, calcium oxalate, calcium phosphate, struvite and cystine are radio-opaque stones, while uric acid, xanthine and hypoxanthine stones are radiolucent.[6]

- **Calcium stone (70–80%)**

1. Calcium oxalate monohydrate (40–60%)
2. Calcium oxalate dehydrate (40–60%)
3. Calcium phosphate (20–60%)
4. Calcium hydrogen phosphate (brushite) (2–4%)
5. Calcium orthophosphate (whitelockite), octacalcium phosphate

- **Uric acid stone (5–10%)**
- **Cystine stone (1%)**
- **Struvite**
- **Mixed stones**

1. Mixed calcium oxalate–phosphate (35–40%)
2. Mixed uric acid–calcium oxalate (5%)

RISK FACTORS FOR THE DEVELOPMENT OF URETRIC STONES:

Genetic causes: Primary hyperoxaluria, cystinuria, Dent's disease,familial hypomagnesemia with hypercalciuria and nephrocalcinosis,Bartter syndrome types III and IV, etc.

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Anatomic abnormalities: Horse shoe kidney, solitary kidney, ureteropelvic junction stenosis, medullary sponge kidney, pyeloureteral duplication, polycystic renal disease, etc.
Epidemiological factors and genetic predisposition: Dietary risk factors, climate, occupation, family history of stones.
Excessive excretion of promoters of urinary crystallization: Calcium (idiopathic hypercalciuria), oxalate (enteric hyperoxaluria), uric acid (uric acid hyperexcretion)
Abnormalities of urinary pH:dRTA, gout, infection stones (struvite stones caused by urea-splitting organisms).
Reduced excretion of inhibitors of urinary crystallization: Hypocitraturia, hypomagnesemia
Metabolic syndrome and obesity: Pure uric acid stones
Low urine volume: Reduced intake or increased loss of water
Hypercalcemic disorders: Primary hyperparathyroidism and other disturbances of calcium metabolism.
Lithogenic drugs: Triamterene, indinavir, sulfadiazine and uricosuric agents.Inflammatory bowel disease and other intestinal malabsorption states**.**[6]

MEDICAL MANAGEMENT OF URETRIC STONE:

Management of uretric stone needs thorough substantivity. Clinical presentation with specific signs and symptoms, deep case history record and laboratory tests and assessments helps for diagnosis, depending on these presentation further treatment is decided either surgical or medical treatment. Medical management is indicated for clinically stable patients with non-obstructive urinary stones, recurrent stone formers and the patients with underlying systemic diseases. Detailed history of patient illness including family history, drug history, and history of previous similar illness and previous interventions needs to be recorded. Assessment of risk factors for stone disease should be carried out. Medical treatment of kidney stones includes dietary management, disease-specific therapies and medical expulsion therapy (MET) of stones.[7]

Dietary management by consuming fluid intake therapy:

Fluid intake and dietary changes are important measures in preventing recurrence of kidney stones. Many trials have shown that increasing urine volume to at least 2 L/day OR 2 lit/day can reduce the recurrence of stone disease by up to 40–50%.[8] Fluid intake mainly should include water. As tea and coffee contain oxalate, milk (which binds free oxalate) should be added to them. However, increasing the urine volume has a disadvantage of reducing urinary citrate.A small reduction in urinary oxalate has been found to be associated with significant reduction in the formation of calcium oxalate stones; hence, oxalate-rich foods like cucumber, green peppers, beetroot, spinach, soya bean, chocolate, rhubarb, popcorn, and sweet potato should be avoided. Many studies have found calcium restriction to increase the risk of stone disease; therefore, dietary calcium restriction is not recommended. Hypocitraturia is a proven risk factor for stone formation and is found in about 16–63% of calcium stone formers.[9,10] Oral potassium citrate (Kcit) has been shown to be useful in increasing urinary citrate and reducing the stone recurrence. Dietary replacement with high citrate as a substitute to Kcit has been studied. Lemon juice when delivered as a lemonade therapy was found to increase urinary citrate.[11]Odvina found orange juice to increase urine pH and urinary citrate.[12] Kang et al. compared 11 patients taking Kcit with 11 matched patients on lemonade therapy and found both the therapies to increase urinary citrate. However, the effect with Kcit was significantly better than the effect with lemonade.[13]

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Diuretic therapy:

Therapies that increase renal fluid output such as diuretics might theoretically facilitate stone passage and elimination because of the associated increased hydrostatic pressure within the ureter. The most effective and best tested diuretic agents are thiazide diuretics which are efficiently used for calcium stones. Reduction of calcium in urine has been attributed to enhanced reabsorption of calcium in the distal convoluted tubule and sodium depletion; the latter effect can be nulliûed by excessive sodium consumption. One complication is thiazide-induced potassium depletion, which causes intracellular acidosis and can counter the hypocalciuricbeneût by producing hypocitraturia. For treating nephrolithiasis, thiazides should always be prescribed with a potassium supplement, either dietary or pharmacological. [14]Potassium citrate is the preferred choice because it provides both potassium and citrate. The theoretical concern of metabolic alkalosis with thiazide-potassium citrate combination has not been shown to arise in clinical trials. Indapamide is as effective as hydrochlorthiazide with potentially fewer side-effects. The potential positive economic impact from diuretic treatment is not insignificant. In the event that the stone does not move, high renal fluid output could also cause a rapid increase in pressure transmitted back into the kidney that could eventually rupture the urinary tract wall and/or result in irreversible renal impairment. Therefore diuretics are not routinely recommended in acute ureteric stone.[15]

Herbal therapy:

In the traditional systems of medicine, most of the remedies for kidney stone management were taken from plants and they were proved to be useful, though the rationale behind their use is not well established through systematic pharmacological and clinical studies except for some composite herbal drugs and plants. Various plant extracts exert their antilithiatic properties by altering the ionic composition of urine, e.g. by decreasing the calcium ion (Table 1). Today, many herbal formulations are commercially available which are used for kidney stone management. The marketed composite herbal formulations, Cystone (Himalaya Drug Company, India), Calcuri (Charak Pharmaceuticals, Bombay, India), Uriflush (Inti Sumatera Global, Indonesia), Uriflow (Discovery Herbs, USA) and Chandraprabhabati (Baidyanath, India) have been widely used clinically to dissolve urinary stones in the kidney and urinary bladder. Pharmacological and clinical studies carried out on a composite herbal formulation, Trinapanchamool consisting of five herbal drugs namely Desmostachyabipinnata, Saccharumofficinarum, Saccharumnunja, Saccharumspontaneum and Imperatacylindrica found it to be effective both as a prophylactic in preventing the formation and as a curative in dissolving the pre-formed stones in albino rats. The antiurolithiatic activity of this formulation has been attributed to its diuretic activity[16]. Cystone is a product of the Himalaya Drug Co. which is often prescribed by the physicians to the patients suffering from urinary calculi. There are various studies which showed its ability to inhibit calcium phosphate and calcium oxalate mineralization. In addition, its efficacy to reduce urolithiasis was also reported in male Wister rats. In various reports, the anticalcifying properties of Cystone are used as a reference for evaluating the antilithiatic properties of other plants.[17]

Table representing Herbal Agents And Their Mechanisms Of Action

Sr.No.	Herbal Agents	Potential Beneficial Actions
1.	Herniariahirsuta	Removes crystals already attached to cell surface, results in higher COD vs COM

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		excretion
2.	Cranberry juice	Increases urinary citrate excretion, decreases urinary oxalate and calcium ion excretion
3.	Grapefruit juice	Increases urinary citrate excretion
4.	Dolichosbiflorus	Decreases calcium phosphate precipitation
5.	Bergenialigulata	Decreases calcium phosphate precipitation
6.	Zea mays	Diuretic
7.	Amnivisnaga	Diuretic
8.	Aervalanata	Decreases urinary calcium, oxalate, uric acid & phosphorus excretion
9.	Costus spiralis	Decreases stone size with unknown mechanism, no diuretic effect

Probiotic therapy:

The discovery of oxalate-degrading bacteria within the human gastrointestinal tract has led to aûrry of research regarding the role of probiotics in the treatment of recurrent calcium oxalate nephrolithiasis. In order to verify smaller studies that demonstrated a lower prevalence of Oxalobacterformigenes in stone formers than in controls, Kaufman et al. evaluated stool samples from 247 recurrent calcium oxalate stone formers and 259 matched controls and found a 17 and 38% prevalence of O. formigenes, respectively. Multivariate analysis revealed a 70% reduced risk of being a stone former if colonized with O. formigenes[18]. Although there was a difference in colonization between stone formers and controls, lack of colonization with O. formigenes cannot be considered as a primary risk factor for calcium oxalate nephrolithiasis as 62% of nonstone formers were not colonized, and urinary oxalate surprisingly did not correlate with the presence or absence of colonization. Intestinal colonization of O. formigenes may account for the development of calcium oxalate nephrolithiasis in select patients, and consequently, it is conceivable that increasing colonization of the gut with oxalate-degrading bacteria could lead to decreased intestinal absorption of oxalate and a corresponding decrease in urinary calcium oxalate. Interestingly, in patients with primary hyperoxaluria, administration of O. formigenes in enteric-coated capsules led to a significant decrease in urinary oxalate, suggesting that oral administration may promote the enteric metabolism of endogenously produced oxalate. Although the reduced urinary oxalate levels and low side effect profile associated with this probiotic are promising, prospective trials must be completed to confirm these findings in stone formers. Indeed, recent promising results from uncontrolled studies showing a reduction in urinary oxalate with the administration of lactic acid bacteria [27] were not confirmed in a prospective randomized, doubleblind,placebo-controlled trial in calcium oxalate stone formers.[19]

Stone-specific therapies:

Calcium oxalate stones: In patients with idiopathic hypercalciuria, thiazide diureticshave shown to reduce the recurrence rates by up to 70%. It is the only medical therapy directed at reducing urinarycalcium. Citrate supplements as detailed earlier areuseful. Pyridoxine sometimes can be useful in patients withprimary hyperoxaluria, but not in idiopathic hyperoxaluria.Oxalobacterformigenes is an oxalate degrading bacteriumfound in human gastrointestinal tract. It is thought thatincreased colonization of the gut might lead to decreasedabsorption of dietary oxalate and decrease in urinaryoxalate excretion. Colonization

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with O. formigenes showedbenefit in uncontrolled studies; however, a prospective,randomized, placebo control, double-blind trial refutedsuch benefits.[20,21]

Uric acid stones: The aim of treatment in uric acid stones is to increase thesolubility of uric acid in urine. It is achieved by increasingthe urine volume and by alkali therapy. Allopurinol is auseful adjunct to the therapy.[21]

Struvite stones: Struvite stones form in alkaline urine from infection withurea-splitting microorganisms. Antibiotics are the mainstayof the therapy with occasional use of acetohydroxamicacid.[21]

Cystine stones: This is a rare stone type. The aim of treatment is toreduce the concentration of free cystine and increase itssolubility in urine. A high fluid intake up to 4-5 L/day OR4-5 lit/day and alkalinization of urine with target urinepH >7 is desirable. Chelating agents like D-penicillamineor tiopronin are indicated when 24-hour urine cystineconcentration exceeds 2000 μmol/l.[21]

General stone-expulsive therapies:

The expulsive therapy for kidney stone management comprises the use of drugs to help the spontaneous passage of ureteral calculi. The ureteral edema and ureteral spasm have been postulated to affect stone passage; therefore these effects have been targeted for pharmacologic intervention. The primary agents that have been evaluated for the expulsion of kidney stones are calcium channel blockers, steroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and α1-adrenergic receptor antagonists.Steroids have been used to reduce mucosal edema and aid in stone passage. NSAIDs also have the potential to decrease inflammation and mucosal edema and are useful for analgesia during stone passage, but have not been proven to be successful in stone passage when used alone[22]. Nifedipine is the most studied calcium channel blocker used to treat ureteral spasm and promotes stone passage [23].The rationale for using α blockers is based on the presence of large numbers of α1 adreno receptors in the distal ureter. Stimulation of the α receptors increases the force of ureteral contraction and the frequency of ureteral peristalsis, whereas antagonism of the receptors has theopposite effects. These blockers inhibit basal ureteral tone and peristaltic frequency and decrease the intensity of ureteral contractions. The likely mechanism that α- blockers use in stone passage has been to reduce ureteral spasm, increase pressure proximal to the stone, and relax the ureter in the region of and distal to the stone[24]. The rationale in using α1 antagonists in expulsive therapy has been that they are capable of decreasing the force of ureteral contraction, decreasing the frequency of peristaltic contractions, and increasing the fluid bolus volume transported down the ureter[25]. Tamsulosin has been the most commonly studied α1-blocker in the treatment of ureteral stones; however, the data have been extrapolated and clinically tested on other α-blockers as well. Tamsulosin has equal affinity for α1a and α1d receptors[26]. The α1d receptor is the most common receptor in the ureter and is most concentrated in the distal ureter.

CONCLUSION:

No standard drug available in spite of intensive research to establish the mechanisms of stone formation, dietary management, expulsive drugs, evaluation of medicinal plants and other agents in the treatment of urinary stones. The main drawbacks in the development of a standard drug

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may be attributed to multi-factorial nature of kidney stones, different biochemical disorders that lead to stones, and different chemical forms of renal stones.Awareness of the advantages and limitations of different modalities of medical therapy is necessary in order to provide the correct treatment to pateints presenting with this common complaint.

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