Urolithiasis: An Update on Diagnostic Modalities and Treatment Protocols

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Urolithiasis or urinary stone disease is a ubiquitous affliction that spares no geographical region or demographic. Plenty of research is being carried out in quest for mitigating this disease condition. However, any detailed information that could impart knowledge on all the major aspects of the subject in an un-fractionated form is still deficient. This review is an attempt to revive the existing knowledge on urolithiasis, basically focused on its diagnosis and treatment and to provide a comprehensive data and up-to-date information on the subject matter. This article also focuses on synthetic drugs and formulations available for the treatment of urolithiasis in the global market and provides a section pertaining to risk factors and dietary preventive measures for urolithiasis.

Key words: Urolithiasis, kidney stone, urine, diagnosis, therapeutic modalities, extracorporeal shock wave lithotripsy

Urolithiasis is a common affliction that is widespread globally. Its roots of existence run deep down to Egyptian mummies dated 4800 BCE, in which kidney and bladder stones were found[1,2]. Urolithiasis is a multifactorial disease wherein stones are formed at any location within the urinary tract with its cause lying in series of events that lead to disruption of equilibrium between promoters and inhibitors of crystallization in the urinary system, *viz.* low volume of urine, urinary pH, presence of calcium, sodium, oxalate and urate known to promote crystallization and citrate, pyrophosphate, magnesium, glycosaminoglycans, urinary prothrombin fragment 1, osteopontin and acid polypeptides that inhibit crystallization[3-6]. There are several approaches for the treatment of urolithiasis that include the use of various synthetic and natural drugs. This review emphasizes on the recent updates on urolithiasis and its treatment protocols and gives an account on various marketed drugs and formulations along with their mechanism of action.

THEORIES ON STONE FORMATION

Free particle theory:

Free particle theory states that the crystals of one of the stone forming constituents spontaneously precipitate out of the supersaturated urine and begin to aggregate or grow in size in the lumen of nephron during the passage of urine through kidney. There are chances that one of these numerous crystals may get retained at some distal or narrow portion of the nephron where it may act as a nidus for stone development[7,8].

Fixed particle theory:

According to the fixed particle theory, crystals that precipitate out of the supersaturated urine get attached to the renal epithelium at the site of renal tissue injury that may be caused due to infectious pathogens or crystals themselves and once attached to the renal epithelium they act as foci for stone formation as are regularly exposed to the supersaturated urine[7,8].

Randall's plaque hypothesis:

Randall's plaque hypothesis considered that stone

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formation takes place at the site of renal lesion. More specifically this hypothesis states that, due to the milieu created as a result of low urinary pH and volume and increased urinary calcium levels, calcium phosphate depositions (apatite), that are a form of renal lesions, originate initially along the basement membranes of thin loops of Henle and then eventually spread to the interstitium and then to the urothelium ultimately eroding the same. These apatite deposits termed as Randall's plaques, on being constantly exposed to calyceal urine due to the loss of urothelium then attract organic substances like lipids, glycosaminoglycans and urinary proteins such as osteopontin and Tamm-Horsfall protein that form a matrix on which accumulate apatite crystals that again get coated with a layer of urinary proteins and other organic substances and so on, forming a multilayered sandwich of apatite and organic matrix. These multiple layers then form an attachment site for calcium oxalate crystals where they eventually grow and form stones[7,9-13].

Blocked lymphatic theory:

The theory explains that renal lymphatic system drains the renal pelvis and prevents accumulation and aggregation of precipitating salts in the kidney. But in case of impairment or destruction of these renal lymphatics, salt precipitates tend to grow into larger concretions during their passage through the lymph vessels and get obstructed at the fornices of the calyces just outside the collecting system where the concretions eventually erode the surrounding membrane ultimately causing urine percolation and then grow into larger renal stones by being in constant contact with the salts and other organic substances in the urine[14,15].

Vascular theory:

Vasa recta and other capillaries in the renal papillary region, due to their repeated bifurcations are prone to quick changes from laminar to turbulent flow of blood, which is similar to as seen with the bifurcated arteries. Owing to this repeated blood flow changes as well as their hyperosmolar and hypoxic milieu, they are exposed to afflictions and injuries and as is case with arteries, these blood flow changes and vulnerable tissue structures result in the formation of atherosclerotic plaques in the vasculature of the renal papilla followed by calcification. These calcareous substances may erode their way into the renal interstitium and papillary ducts of Bellini where they grow into larger stones on being in constant contact with the urine[16].

CLINICAL PRESENTATION

Urolithiasis may exist asymptomatically, but it is often presented by excruciating pain that originates from the flank and radiates to the genitals. Pain is produced as a result of stone obstruction usually at uretro-pelvic junction, pelvic brim and vesico-ureteric junction. Stone obstruction also produces lower abdominal cramps, dysuria, urinary urgency and strangury, and also promotes the elevation of intrarenal pressure that induces prostaglandin synthesis, which again causes ureteric smooth-muscle spasm. Renal colic is generally associated with nausea and vomiting. Haematuria and infection are also common symptoms associated with renal stone disease. Urinary tract infection (UTI) may be a result of stone obstruction or may be the cause of magnesium ammonium phosphate (struvite) stones also called the infection stones[17-19]. Fever, chills and pus formation are usually associated with infection stones[17,20,21].

DIAGNOSTIC INVESTIGATIONS

Investigating medical history, family history and dietary history of the patient also aids in diagnosis. Medical history may unveil the medical conditions the patient is suffering from or any medication or medical therapy the patient is recently adhering to or underwent that might be the predisposing factors for urolithiasis. Any family history of renal stone disease and food habits of the patient may further help in revelation of the disease and determining the potential cause[22]. Intolerable flank pain and haematuria though typical of renal stone disease, are not ideally a confirmation for the presence of stones in the urinary tract. In order to rule out the false alarm and confirm the presence of renal stones, it is practically indispensable to carry out a series of under mentioned diagnostic evaluations.

Urine analysis:

It is the first investigative step for diagnosing the presence of stones in the urinary tract. It includes visualisation of the presence of blood and determination of urine volume, pH, calcium, creatinine, sodium, phosphate, oxalate, citrate, uric acid and cystine levels in urine[20,23]. Urine analysis includes evaluation by appearance, dipstick, chemical tests and microscopic examination. Cloudy appearance of urine usually accounts for the presence of bacteria and pus; and reddish urine is indicative of haematuria. Dipstick analysis usually helps in determining the pH and specific gravity of urine and determining the presence

of protein (albumin), blood, leukocyte esterase and nitrite in urine[24,25]. Urine pH is sometimes indicative of the type of stone present, like it is well established that acidic pH is favourable for uric acid and cystine stone formation, while alkaline pH promotes struvite and calcium phosphate stone formation[17,24,26]. Pus in urine usually indicates infection. If pus is associated with alkaline urine it clearly establishes presence of struvite stones, but if pus is found in acidic urine, it can be deduced that the infection is secondary and that the stone present may be organic i.e. either uric acid stone, cystine or xanthine stone[27]. Urine culture is usually performed to confirm the presence of UTI[23]. Microscopic examination is undertaken to look for the presence of white blood cells (WBCs), red blood cells (RBCs) and stone forming crystals. Elevated WBC count again is an indicative of UTI while elevated RBC count indicates haematuria[24,25]. Different shapes of stones appear in microscopic examination *viz*. dumbbell shaped calcium oxalate monohydrate crystals (COM), tetrahedral or bipyramidal shaped calcium oxalate dihydrate crystals (COD), calcium phosphate stones appear narrow and elongated, struvite stones appear as coffin lid like rectangular prisms, uric acid stones appear like yellow or reddish brown diamond shaped crystals (rhomboidal) or as needles, cystine stones appear hexagonal[24,26,28,29] while 2,8-dihydroxyadenine stones appear as brown colored spherical crystals[30]. Evaluation of urine for presence of components such as calcium, creatinine, sodium, phosphate, oxalate, citrate, magnesium, uric acid and cystine helps in the determination of the causal metabolic abnormalities and risk factors[18].

Stone analysis:

Stone analysis forms a crucial part of investigation in recurrent stone formers, wherein it provides a picture of mineral constituents of stones and thereby, of the factors and metabolic disorders that may be associated with stone formation and thus helps in proper medical intervention. Stone analysis involves examining the entire crust and core of stones in quest for the stone components and their respective location in the stone and then summarizing the same to strategically deduce the underlying cause and hence direct the diagnosis and treatment. X-ray crystallography and infrared spectroscopy are most popular techniques for stone analysis[31,32].

Serum analysis:

Serum analysis includes determination of serum levels of urea, uric acid, creatinine, sodium, potassium, bicarbonate, albumin, calcium, magnesium and phosphate, which serve as indicators of renal function and underlying metabolic causes[17,33]. Serum urea, uric acid and creatinine levels provide a picture of glomerular filtration rate and renal tissue integrity that are adversely affected in renal stone disease[34]. If elevated levels of calcium are detected in serum, serum levels of parathyroid hormone need to be determined so as to investigate for hyperparathyroidism[22]. Apart from serum analysis, haematological analysis is performed to detect leukocyte count, as leukocytosis is apparent in patients with infection[17].

Imaging:

Imaging is the most important diagnostic tool that offers confirmation of the diagnosis made on behalf of the familial history, physical examination and laboratory tests. It provides ample information about stone and plays a crucial role to determine the type of treatment one should opt for[35]. Kidney-Ureter-Bladder (KUB) Radiography is one of the preliminary imaging studies, which principally is a plain X-ray of abdomen. It helps in locating the stones and visualizing their number, shape and size. It is more compatible in detecting calcium rich stones that are radiopaque as compared to the less radio-dense uric acid, struvite and cystine stones. Although, it is very economic but, bowel gas, stool and extra-urinary calcifications highly limit its efficiency and hence its applicability. Moreover, it carries high risk associated with radiation exposure[18,36]. However, it continues to be frequently used for preliminary detection, for fluoroscopically guided shock wave lithotripsy and further for eventual follow ups[37].

Ultrasound is an imaging modality that uses high frequency sound waves that echo or bounce back in the presence of solid structures such as stones creating an image of the same. Real-time ultrasound is now being used as a first-line imaging technique for urolithiasis during pregnancy, as it does not involve risks of radiation exposure like teratogenicity, mutagenicity and carcinogenicity to the foetus[38,39]. It is also the imaging tool of choice for detecting and locating renal stones in children[39]. The technique is very cost effective and can detect all types of stones except for its incapability of detecting ureteral calculi[6].

Intravenous Pyelography (IVP) is a technique in which iodinated contrast media is administered to the patient intravenously that travels in blood and ultimately

gets filtered from the kidneys and cleared from the ureters and bladder during micturition. Meanwhile, series of X-rays of the kidneys, ureters and bladder are taken at defined intervals where the contrast media provides a clear picture of the structure and function of the urinary system and of any obstruction or stone therein[40]. It is well versed in locating the stone and providing information not only about the shape and size of the stone but also its environment and extent of obstruction along with the anatomy and functioning of the kidneys. Although, its specificity and sensitivity is greater than ultrasonography and KUB radiography, still its acceptability is on constant decline owing to the potential adverse effects associated with the contrast media that range from nausea, flushing, bradycardia to nephrotoxicity and anaphylactic reactions[36]. It is contraindicated in patients with impaired renal function, contrast medium allergy, pregnant women and patients on metformin medication[6,41].

Computed tomography (CT) utilizes X-ray beam for imaging, which is rotated around the patient's body to produce series of images followed by three dimensional reconstructions of the images. Noncontrast helical CT has become increasingly popular owing to its speed, accuracy and its efficiency in detecting all types of stones at any location, that too without any need for administration of contrast media. It is on the verge to outweigh all other imaging techniques and has largely replaced IVP. It is known to have sensitivity and specificity of 96-100% and accuracy of 96-98%[2,36,42,43]. It has advantage of providing information about the stone composition, extent of obstruction, renal anatomy and physiology and any extra-urological or alternative causes of flank pain such as appendicitis, pancreatitis and gynaecologic aberrations[18,44]. The only drawback of this technique is the high amount of ionising radiations required for imaging that limits its use majorly in pregnant women and children. To overcome this, low-dose unenhanced CT and dual-energy CT (DECT) have been introduced lately. DECT possesses two X-ray sources and two detector units and utilizes differences in X-ray attenuation properties of the constituents of stones for determining the mineral composition of stones. Stones appear in varied colors depending upon their type, when viewed by DECT[43-46].

Digital tomosynthesis is a recently introduced imaging technique. It has been found to be associated with considerable less risk of radiation exposure as compared to the widely used noncontrast CT and may come up with more benefits and wider acceptance[47].

Isotope renography or nuclear imaging is an imaging tool that involves intravenous administration of a radiopharmaceutical substance labelled with technetium-99 and detection of the emitted radiations by the gamma camera as the radioactive substance travels down the urinary tract providing images of the same[17,39,40,48].

Magnetic resonance imaging uses magnets, radio waves and body's natural magnetic properties for imaging urinary stones, and sometimes requires administration of paramagnetic contrast media for the same[39,40,44,49,50]. It found applicability in visualising pathological changes caused by stones in the urinary tract of paediatric and pregnant patients owing to its superior soft tissue contrast and for it does not carries risk associated with ionizing radiations[38,50], until high doses of paramagnetic contrast were found to be teratogenic[44]. But it has proved to be a safer alternative with no mandatory requirement for administration of contrast media[38].

TREATMENT PROTOCOLS

Once the presence of urinary stones is confirmed and their location, size and type is established, medical intervention comes into play that includes treatment by drug therapy or surgical removal of the stones depending upon their size, shape, location, type and other pathological conditions.

Non-steroidal antiinflammatory drugs (NSAIDs) and opioids are the preferred classes of drugs for relieving pain associated with urolithiasis. Both the categories of drugs have been found to be equally effective although NSAIDs are known to cause potential gastrointestinal and renal side effects while opioid analgesics require administration of antiemetic agents as they are known to cause nausea and vomiting along with urinary retention, constipation and respiratory depression. Opioids are also associated with the risk of addiction on long term use[51-54].

Medical expulsive therapy (MET) is used to allow spontaneous expulsion of moderately sized distal ureteral calculi from the urinary tract. Alpha-adrenergic blockers or calcium channel blockers with or without corticosteroids are used for MET. By blocking α-receptors and calcium influx of the urinary tract respectively, α-adrenergic blockers and calcium channel blockers produce outward expulsion of the stones by inhibiting ureteral smooth muscle contractions thus

facilitating elevation of hydrostatic pressure near to the stone along with providing symptomatic relief from renal colic as well. Tamsulosin is the drug of choice for MET owing to its better tolerability, though doxazosin and terazosin are equally effective. Corticosteroid addition to tamsulosin has been found to be very efficacious as corticosteroids act as antioedema agents and also aid in alleviating renal colic[2,55-60].

Thiazide and related diuretics are indicated in renal stone disease associated with idiopathic hypercalciuria. They are known to produce hypocalciuric action by enhancing reabsorption of calcium at proximal and distal convoluted tubule. Problem with the use of thiazide diuretics is their universally known potassium depletion causing hypokalaemia, which can ultimately lead to hypocitraturia, a factor responsible for augmenting urolithiasis, which could be corrected by potassium citrate or amiloride supplementation. Potassium-sparing diuretic, triamterene can also be used to correct hypokalaemia but it possesses the risk of producing triamterene stone, a type of drug stone owing to its low solubility[61-64].

Allopurinol is prescribed for the treatment of calcium oxalate and uric acid stones. Being a xanthine oxidase inhibitor it inhibits uric acid production from hypoxanthine and xanthine thus reducing urate levels in urine, which again turns out to be inhibitory for nucleation of calcium oxalate[65-67]. Febuxostat is also a xanthine oxidase inhibitor like allopurinol but has been found to be more efficacious in reducing urinary urate levels as compared to allopurinol[21].

Potassium citrate basically raises urinary citrate levels. Citrate complexes urinary calcium to a soluble form, thus inhibiting calcium phosphate and calcium oxalate crystal aggregation. Potassium citrate also tends to inhibit uric acid stone formation owing to its alkalinizing effect on urine[67-69]. Unlike sodium citrate and sodium bicarbonate, it does not tend to raise sodium load, which is known to increase calcium excretion and produce citrate reduction in urine and is therefore preferred over them[66]. But, it does possess tendency for producing gastrointestinal upset[69]. Potassium citrate, allopurinol and thiazide diuretics are known to reduce stone recurrence rates as well[70].

Sodium cellulose phosphate is known to bind to intestinal calcium and thus inhibit absorption of calcium leading to reduction in the elevated calcium excretion thus reducing calcium stone formation. It has been found to be efficacious but has potential to cause hyperoxaluria and hypomagnesaemia, which again are vital for exacerbating renal stone disease. Sodium cellulose phosphate can also cause parathyroid stimulation[71,72].

D-penicillamine is used in case of cystine stones for treating cystinuria. By forming penicillamine-cysteine heterodimers that are comparatively more soluble than cysteine-cysteine homodimers, it promotes dissolution of cystine stones and lowers cystine levels in urine. However, it is of limited use owing to its potent adverse effects which include, nephrotic syndrome, leukopenia, thrombocytopenia, neuropathy, dermatitis and pancytopenia.

Alpha mercaptopropionylglycine (or tiopronin) is a better tolerated alternative to D-penicillamine, but its efficacy and availability is very less as compared to D-penicillamine[30,62,66,73,74].

Acetohydroxamic acid is prescribed in case of struvite stones that are usually formed due to or are associated with the UTI caused by urease producing organisms. Acetohydroxamic acid being a urease inhibitor seems to be beneficial in these types of infection stones but its efficacy is challenged by its potential adverse effects that include deep vein thrombosis, haemolytic anaemia, gastrointestinal distress, tremors and alopecia[51,66,71].

An interesting anaerobic bacterium *Oxalobacter formigenes*, found in human gastrointestinal tract, is prescribed for idiopathic stone disease wherein its increased colonization in the gut is known to enhance catabolism of intestinal oxalate to formic acid and carbon dioxide, ultimately leading to reduced urinary oxalate levels. *O. formigenes* has emerged as a promising agent for urolithiasis associated with primary hyperoxaluria. Investigations on larger scale prior to its wider use are necessary and are ongoing[75-79].

Chemolytic dissolution therapy is a dissolution technique that aims at the dissolution and removal of urinary stones via pH alteration, chelation and disulphide rearrangement[80]. Chemolytic dissolution may be systemic (oral or intravenous) or direct (irrigative)[81]. Systemic chemolysis of uric acid stones is achieved by raising urinary pH by administering potassium citrate or sodium bicarbonate[39,80]. Immediate alkalinisation can also be achieved by acetazolamide, a carbonic anhydrase inhibitor; although its applicability is limited because of its capability of producing calcium phosphate stones[82]. Acetohydroxamic acid is commonly used for the oral dissolution of struvite stones, which is known to act

by inhibiting urease production by bacteria, an enzyme that splits urea to produce ammonia, which then combines with trivalent phosphates to produce struvite stones[74], but it has a potential to cause haemolytic anaemia[80]. Systemic chemolysis of cystine stones is achieved by chelation with the help of D-penicillamine or α-mercaptopropionylglycine. When urinary tract stones seem to be unresponsive to the oral chemolytic therapy, direct chemolytic dissolution is opted for, which involves irrigation of the urinary system with chemolytic fluids by means of nephrostomy catheters (percutaneous nephrostomy) or ureteric catheters and duration of irrigation ranges from days to weeks. Chemolytic fluids commonly used are hemiacidrin, renacidin and Tham-E (tris[hydroxymethyl] aminomethane). Renacidin, which is generally used for the dissolution of struvite stones, is a multielectrolyte solution consisting mainly of citrate, malonate and gluconate that provide citrate and magnesium for chelation and dissolution of calcium and phosphate. It is potentially corrosive to the urothelium and has caused deaths earlier due to urosepsis, but is used successfully with antibiotics. Tham-E is the most popular agent for dissolution of cystine stones and requires nephrostomy catheters for the same[66,81,83-85]. Chemolytic dissolution therapy can be used as an adjunct to ESWL and PCNL, or can also be used to completely avoid surgery[86]. Commonly used synthetic drugs are listed in Table 1[87-94]. Stones that are large in size or possess staghorn contours or are very proximal in location and also are unresponsive to medical therapy require surgical intervention or more correctly, active stone removal[95].

Extracorporeal shock wave lithotripsy:

Extracorporeal shock wave lithotripsy is a minimally invasive and very popular technique for active stone removal. It is basically a fragmentation technique that utilizes shock waves originating from a lithotripter for fluoroscopically guided stone fragmentation in a patient lying in water-filled or gel filled cushion that acts as a transition medium for transferring shock waves inside the patient's body. Stone fragments thus generated are small enough to eventually drain out of the body along with the urine. A lithotripter may utilize electromagnetic, electrohydraulic or piezoelectric source of energy for generating shock waves[6]. It can be effectively used for disintegrating renal pelvic or calyceal stones of size upto 2 cm in diameter and now it is also being used for fragmenting struvite stones, staghorn stones and ureteric stones as well[96,97]. It's important foredeal is that it does not require anaesthesia and can be performed on outpatient basis, an important factor for patient acceptability[98]. As is the case with every remedy, this tool of stone fragmentation that has revolutionised the treatment options available for renal stone disease is also not debarred of possessing harmful effects, the most important being its potential to enhance stone recurrence. Renal tissue injury, haemorrhage and left out residual stone fragments are other related complications[6,72,97]. Recently a third generation electromagnetic shock wave lithotripter, the Lithoskop® was introduced which was found to be associated with fewer complications as compared to the existing lithotripters[99].

Ureteroscopy:

Ureteroscopy is a minimally invasive technique that utilizes a flexible fiberoptic ureteroscope that passes through urethra via bladder up to the ureter for accessing

TABLE 1: SYNTHETIC DRUGS FOR UROLITHIASIS

Drugs/Synthetic molecules	Stones treated
Thiazide diuretics[61,62,64,67] (hydrochlorothiazide, trichlormethiazide, chlorthalidone, indapamide)	Calcium oxalate, calcium phosphate stones
Potassium phosphate[66,87]	Calcium oxalate stones
Sodium cellulose phosphate[71,72]	Calcium oxalate stones
Allopurinol[65,82]	Uric acid stones
D-penicillamine[66,73,88]	Cystine stones
Febuxostat[89-91]	Uric acid stones
Potassium citrate[68,71]	Calcium oxalate, uric acid stones
Alpha blockers (tamsulosin, terazosin, doxazosin)[66,92]	Ureteral stones
Alpha mercaptopropionylglycine[66,88]	Cystine stones
Acetohydroxamic acid[66,71]	Struvite stones
Calcium channel blockers (nifedipine)[55]	Ureteral stones
Acetazolamide[21]	Uric acid, cystine stones
Sodium bicarbonate[66, 93]	Uric acid stones
NSAIDs (diclofenac, indomethacin, ketorolac, ibuprofen)[19,94]	All stone types

the entire renal collecting system[96,100-102]. It is equipped for extracting smaller stones as well as fragmenting larger ones using ballistic and laser (holmium: yttrium-aluminium-garnet laser/holmium: YAG laser) lithotripsy[17,96,101] due to which it has become a popular modality for treatment of urolithiasis in children and getting wider acceptance in pregnant women as well as in patients after urinary diversion[96,103,104]. Although, now in constant decline with the advent of more flexible and narrow ureteroscopes; ureteral injury and perforation, steinstrasse, haematuria and infection are the complications that are associated with ureteroscopy[96]. Even flexible ureteroscopes are at a verge of becoming a thing of past as robotic flexible ureterorenoscopy is in line, which is operated using robots relieving doctors of the troublesome and tedious task of holding flexible ureteroscopes for very long duration during ureteroscopic procedures[105,106].

Percutaneous nephrolithotomy (PCNL):

PCNL is another modality for fragmentation and extraction of stones that requires an incision to be made in the back and dilatation of the tract for the insertion of nephroscope in order to access stones in renal pyelocalyceal system and proximal ureters[107-110]. It is considered a good treatment choice for stones larger than 2 cm in diameter located in renal pelvis or calyx and also for multiple stones[107]. Its most adverse complication is haemorrhage and damage to adjacent organs that hindered its acceptance especially in children[96,107,111]. But, miniaturisation of nephroscopes and introduction of holmium: YAG laser and smaller pneumatic lithoclasts have led to wider acceptance of PCNL and its utilisation for fragmenting smaller stones[96,112].

Laparoscopic surgery:

Laparoscopic surgery is a comparatively invasive technique that requires three to four incisions to be made in order to insert hollow tubes known as ports through which instruments can be passed in order to perform surgery. Sometimes a nephroscope is passed through one of the ports for stone visualization and removal. Laparascopic surgery, although less frequently performed now, is indicated in cases where urolithiasis is associated with renal abnormality or other complications and in cases where minimally invasive advanced techniques fail to offer any relief[17,113,114].

Open surgery:

Open surgery for stone removal requires a single but large incision to be made in order to access the stone. It is associated with lot of blood loss and is followed by excessive pain. It is indicated in case where stone burden is more complicated or is associated with the case of renal transplantation, where the patient is suffering from morbid obesity or possesses anatomical abnormalities and where other advance modalities do not seem to render patient stone free[102,115].

Apart from synthetic formulations and surgical interventions, herbal remedies also form a crucial integral part of the treatment strategies for urolithiasis. Owing to its cost effectiveness, better tolerability and multiple targets of action, phytotherapy proves to be a very beneficial and widely accepted modality for prevention and treatment of renal stones. In fact, phytotherapy is safer and has potential for the prevention of reoccurrence of kidney stones[116].

PREDISPOSING FACTORS AND PREVENTIVE DIETARY MODIFICATIONS

Being a multifactorial disorder, multiple risk indices are associated with the formation of urinary stones that can be broadly categorized as dietary, urinary, metabolic and miscellaneous risk factors.

Dietary risk factors include higher consumption of oxalate, sodium chloride salt and protein (animal protein) rich diet[117] and low intake of fluids[118-125]. Low fluid intake results in highly saturated low volume urine, which is a predominant factor for the formation of all types of stones[123]. Urinary risk factors include low urine volume, hypercalciuria, hyperoxaluria, hypocitraturia and hyperuricosuria[118]. Metabolic predispositions that highly contribute to urinary stone formation include disorders like idiopathic hypercalciuria, primary hyperparathyroidism, Cushing's syndrome, primary hyperoxaluria, hyperuricosuria, cystinuria and hyperchloremic metabolic acidosis[121]. Miscellaneous risk factors include obesity as high body mass index (BMI) is known to be associated with high urinary oxalate, calcium and uric acid levels[126]; diabetes mellitus, which is known to promote formation of uric acid stones[127]; family history of urolithiasis[118,128]; UTI that induce formation of struvite stones; chronic consumption of drugs like triamterene, ceftriaxone, topiramate, indinavir and probenecid that eventually lead to the formation of drug stones; genetic disorders like xanthinuria, primary hyperoxaluria and idiopathic renal hyperuricosuria; structural aberration of the urinary system like that in polycystic kidney disease and

medullary spongy kidney that are generally associated with urinary stasis[121]; hot climatic conditions that cause dehydration and perspiration, ultimately leading to highly supersaturated low volume urine that again promotes stone formation[129-131].

High fluid intake is the mainstay of the preventive measures for urolithiasis as it increases volume and reduces supersaturation of urine, a factor that influences the genesis of all stone types. Moreover, increased fluid intake accounts for increase in voiding frequency, which is desirable to avoid retention of precipitating solutes as well as to avoid the crop up of infection in the urinary tract[132]. In this respect, water is most important of all fluids as it is economic and available.

Dietary oxalate, salt and animal protein restriction together with adequate dietary intake of calcium aids in reducing incidences of urinary stones. Calcium in diet but not calcium supplements have been shown to enhance intestinal oxalate absorption and thus reduce calcium oxalate precipitation in urine[133-135]. Restriction of vitamin C (ascorbic acid) supplements and consumption of vitamin B6 (pyridoxine) rich food pose their own advantages as ascorbic acid can lead to the formation of oxalate when metabolized while pyridoxine prevents formation of oxalate from glyoxylate owing to its role in transamination reaction of glyoxylic acid to glycine[134,136].

Keeping a close eye on one's body weight, maintaining healthy routine and healthy diet that includes vegetables, fruits, fibres and adequate amount of fluids is always a good call not only when it comes to preventing urolithiasis but any disease condition, because these are the indices that when compromised might lead to one or the other health impairments.

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